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14. ABSTRACT

This annual report presents the progress made, to date, in understanding the influences of early Parkinson's disease on all major sensory systems in the same subject cohort. Altered function has now been demonstrated in various sensory domains, most notably olfaction, taste, and vision. Touch and hearing appear not to be influenced by PD, although more data are needed to adequately power these elements of the study. The early sensory alterations found in this study appear to be uninfluenced by L-DOPA repletion.

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INTRODUCTION TO THE REPORT

Parkinson's disease (PD) has been associated with altered sensory function. However, the relative degree of sensory dysfunction in each sensory modality is unknown and no study has assessed sensory function in the same cohort of early stage PD patients. Thus, it is not clear which, if any, of the sensory deficits are correlated with one another. It is also generally unknown as to what degree dopamine repletion mitigates the various sensory anomalies. The goals of this case-control study are to definitively establish, in the same early-stage PD cohort, (a) the nature of the PD-related anomalies that occur in vision, hearing, smell, touch, taste, and balance, (b) which, if any, of the anomalies can be mitigated by dopamine therapy, (c) the relationships of the anomalies with one another, (d) the relative sensitivity of the various sensory tests in discriminating between patients with early PD and controls, and (e) whether the sensory changes, individually or in combination, rival or exceed the sensitivity of *in vivo* SPECT dopamine transporter imaging in detecting early PD. By the end of this 4-year program, extensive sensory data will have been obtained from 40 patients with recently diagnosed early-stage PD and 40 healthy matched controls, resulting in a definitive assessment of the influences of PD and dopamine repletion on all five major sensory systems.

BODY OF THE REPORT

In this second annual report we present the results obtained to date on our extensive sensory testing ofof newly-diagnosed Parkinson (PD) patients and matched healthy controls. We also present the results of the SPECT imaging of their dopamine transporter levels. A consistent picture is beginning to emerge with regard to the first two of the objectives of the program listed above. Our preliminary analyses strongly suggest that PD patients show clear deficits in smell, taste, and vision. In no case does there appear to be a clear indication of improvement following dopaminergic therapy. The influences of PD on the other sensory systems we are testing appear more enigmatic and larger sample sizes and statistical power are needed to definitively establish the degree to which they are influenced by PD. In this progress report, we also present some initial progress towards integrating measures to achieve our other three objectives, i.e. those examining the relation between different sensory deficits and evaluating their sensitivity for early detection of PD.

1. Subjects

This report is based on preliminary results from ten PD and six control subjects, most of whom were tested during two 4-day-long test sessions, once without dopamine repletion therapy and once with dopamine repletion therapy. Motor ratings were performed on all subjects, including the Unified Parkinson Disease Rating Scale (UPDRS), Hoehn and Yahr Scale (H&Y) and Schwab and England ADL Scale (S&E). All contrl subjects were entirely free of motor symptoms (UPDRS score < 2, H&Y = 0, S&E = 100%). A careful family history was taken to insure that that no first-degree relatives had PD or any other neurodegenerative disease. All PD patients were rated with mild PD motor characteristics (UPDRS score < 25, H&Y $\leq$ 2, S&E $\geq$ 90%) and were newly diagnosed with a history of motor symptoms of less than three years. All subjects were evaluated with respect to a large number of exclusion criteria based on diagnostic considerations and factors that could affect sensory-test performance or radiological imaging.

The demographics of the subjects upon which this report is based are presented in Table 1. Although there are some differences between the PD and control subjects, as enrollment increases the two groups will be well equated on these measures. Some of these measures, such as age, will be used as covariates in subsequent analyses to more clearly establish subtle influences of PD on our sensory measurements. .

Table 1: Demographic Characteristics of enrolled subjects

Characteristics	PD cases (N=10) Mean (SD)	Control (N=6) Mean (SD)
Age (yrs)	61.8 (5.3)	63.2 (6.2)
Education (yrs)	17.0 (1.8)	15.3 (5.0)
	n (%)	n (%)
Gender		
Male	7 (70)	3 (50)
Female	3 (30)	3 (50)
Ethnicity		
Caucasian	9 (90)	4 (66.7)
Afro-American	1 (10)	2 (33.3)
Smoking history		
Non-smoker	6 (60)	3 (50)
Past smoker	4 (40)	3 (50)
Current smoker	0 (0)	0 (0)
Alcohol history		
Nondrinker	3 (30)	2 (33.3)
Drinker	7 (70)	4 (66.7)

The two 4-day sessions separated by approximately six weeks, each of which involved the full set of sensory tests and SPECT imaging. For PD subjects, one session occurred while on dopaminergic therapy and the other while off dopaminergic therapy, allowing us to assess the effects of such therapy on the test measures. None of the controls received dopamine. A comparison of the control subject data between the two sessions allows for a determination of test-retest reliability of the sensory and imaging measures, the potential effects of retesting on the sensory measures, and for a clear comparison between PD and control subjects matched on the basis of age-, sex-, and ethnicity. At the time of this analysis, eight of the ten PD and three of the six control subjects had completed both the drug-free and L-DOPA test sessions. In the original protocol, all PD patients were to be first tested prior to dopaminergic therapy. An amended protocol now allows us to test patients first when on medication and then following a period of drug abstinence. This protocol modification not only has facilitated subject accrual numbers, but allows for the counterbalancing of the order of the drug and non-drug testing. With increasing subject accrual, both test orders will eventually be equally represented.

2. Olfaction

The preliminary results from the test of our extensive olfactory test battery are described below, and include tests of odor identification, detection, distrimination/memory, hedonics, and inhibition of sniff magnitude upon smelling an unpleasant odorant. Event-related brain potentials in response to precisely timed pulses of odorants embedded in an air stream of constant pressure, temperature, and humidity are also described. These potentials are established by our capability of presenting discrete pulses of odorants in a humidified airstream using a dynamic air-dilution olfactometer unique in the United States to our Center.

2a. Odor Detection, Identification, and Discriminaton/Memory Test Results

The results of the detection, identification, and discrimination/memory tests are presented in Table 2. The phenyl ethyl alcohol (PEA) threshold scores, measured for each nostril and for both nostrils combined, are determined by a staircase paradigm. Each score indicates the logarithm of odorant concentration at threshold, so larger negative values reflect greater sensitivity. University of Pennsylvania Smell Identification Test (UPSIT) scores for the left and right nostrils are based on the testing of 20 odorants per nostril (i.e., 2 booklets of the 4 10-item booklets of the test), whereas the match-to-sample Odor Discrimination/Memory Test scores are based upon 16 trials per nostril, averaged across 3 delay intervals. As can be seen, PD patients were generally deficient in their performances on all three of these tests and no evidence of influences of dopaminergic therapy was present.

Table 2: Comparison of odor detection and identification test scores between PD and control subjects

Test Measure	Session	PD cases (N=10) Mean (SD)	Control (N=6) Mean (SD)
UPSIT Score			
Left	No Dopamine	8.6 (4.9)	15.8 (2.9)
	Dopamine	11.4 (4.0)	15.0 (3.5)
Right	No Dopamine	11.3 (5.2)	15.8 (3.1)
	Dopamine	10.3 (4.3)	16.0 (2.7)
PEA score			
Left	No dopamine	-3.0 (1.3)	-4.5 (1.2)
	Dopamine	-3.3 (1.7)	-4.6 (2.8)
Right	No Dopamine	-4.2 (2.6)	-4.6 (0.9)
	Dopamine	-3.3 (1.3)	-4.8 (2.6)
Bilateral	No Dopamine	-3.3 (1.7)	-6.2 (2.4)
	Dopamine	-3.0 (0.9)	-5.0 (1.0)
OMT score			
Left	No Dopamine	4.3 (2.2)	8.2 (2.9)
	Dopamine	4.6 (2.4)	7.7 (1.5)
Right	No Dopamine	5.6 (2.0)	8.0 (2.4)
	Dopamine	5.1 (1.4)	7.3 (2.5)

2b. Intensity and pleasantness

Table 3 shows the results of the intensity and pleasantness ratings given to the four concentrations of pentyl (amyl) acetate. No differences were found between the PD and control subjects for either rating, either in overall level or change with intensity. Nor was an effect apparent of dopaminergic therapy on the ratings of PD subjects. Interestingly, despite clear deficits on all other measures of olfaction, the PD subjects showed an increase in intensity ratings with increased odorant concentration that was equivalent to that of the control subjects. The reliability of this finding will be ascertained as more data are collected. While it seems that higher intensity and unpleasantness ratings were given by the PD patients when on dopamine, these same general trends appear in the controls, suggesting a session order effect. This difference will presumably drop away once the session test order is fully counterbalanced.

Table 3: Comparison of odor intensity and hedonic ratings between PD and control subjects. Rating scale values range from 1 to 5, with 5 being most intense or most unpleasant. Concentrations of pentyl (amyl) acetate) are in log vol/vol dilutions.

Rating	Odorant Concentration	Side	PD Session	PD (N=10) Mean (SD)	Control (N=6) Mean (SD)
Intensity	10^{-1}	L	DA	5.0 (1.9)	5.0 (1.4)
			No DA	4.5(1.4)	4.7(0.9)
		R	DA	5.9 (2.2)	5.5 (1.0)
			No DA	5.0(1.3)	5.9(1.9)
	10^{-2}	L	DA	3.8(1.1)	4.5(1.8)
			No DA	3.6(1.9)	2.9(0.2)
		R	DA	4.6(1.9)	4.1(1.3)
			No DA	4.0(1.5)	3.7(1.3)
	10^{-3}	L	DA	2.6(0.9)	2.7(1.5)
			No DA	2.0(1.2)	1.7(0.5)
		R	DA	2.8(1.3)	3.2(1.7)
			No DA	2.1(0.5)	1.9(0.5)
	10^{-4}	L	DA	2.1(1.0)	2.3(1.5)
			No DA	1.5(0.5)	1.4(0.3)
		R	DA	2.4(1.1)	2.3(1.4)
			No DA	1.7(0.7)	1.1(0.1)
Pleasantness	10^{-1}	L	DA	4.8(0.6)	5.4(1.2)
			No DA	5.3(0.7)	4.7(1.4)
		R	DA	4.4(1.1)	4.9(1.3)
			No DA	5.0(1.1)	2.7(0.7)
	10^{-2}	L	DA	5.2(0.5)	5.3(1.1)
			No DA	5.6(1.1)	5.5(1.1)
		R	DA	4.8(0.8)	5.7(1.0)
			No DA	5.7(1.3)	5.1(1.5)
	10^{-3}	L	DA	5.1(0.3)	5.2(0.2)
			No DA	5.1(0.1)	5.3(0.3)
		R	DA	5.1(0.8)	5.2(0.6)
			No DA	5.1(0.3)	5.2(0.5)
	10^{-4}	L	DA	5.0(0.2)	5.1(0.3)
			No DA	5.0(0.0)	5.1(0.1)
		R	DA	5.0(0.6)	5.2(0.4)
			No DA	5.0(0.1)	5.0(0.0)

Unpublished data.

2c. Sniff magnitude

The sniff magnitude ratios obtained for the Sniff Magnitude Test are shown in Table 4. The numbers represent a ratio of the size of a sniff when an odor is encountered divided by the size of a sniff to non-odorous air. Numbers less than one indicate suppression; i.e., inhibiting the size of a sniff upon encountering an odor. Note that the controls inhibited sniffs to odors, most of which were unpleasant, whereas the PD patients generally did not, implying lessened smell sensitivity. Note also that in some cases more suppression occurred on the first than the second presentation of an odorant, likely reflecting a lessened tendency to sniff in a bad odor once such an odor has been previously experienced.

Table 4: Sniff Magnitude Ratios for PD Patients and Normal Controls

Trial	Odor	PD Session	PD (N=10) Mean (SD)	Controls (N=6) Mean (SD)
T1	Butanol	DA	1.00 (0.00)	1.00 (0.00)
		No DA	1.00 (0.00)	1.00 (0.00)
	Ethyl Mercaptoproprionate	DA	1.04 (0.23)	0.85 (0.22)
		No DA	0.96 (0.22)	0.73 (0.16)
	Amyl Acetate	DA	1.06 (0.29)	0.91 (0.23)
		No DA	0.95 (0.12)	0.82 (0.09)
	Methylthiobutyrate	DA	1.08 (0.30)	1.06 (0.19)
		No DA	1.01 (0.15)	0.85 (0.09)
T2	Butanol	DA	1.00 (0.00)	1.00 (0.00)
		No DA	1.00 (0.00)	1.00 (0.00)
	Ethyl Mercaptoproprionate	DA	0.97 (0.24)	0.95 (0.15)
		No DA	1.08 (0.17)	1.05 (0.17)
	Amyl Acetate	DA	0.97 (0.14)	0.97 (0.10)
		No DA	1.03 (0.15)	0.96 (0.23)
	Methylthiobutyrate	DA	0.91 (0.11)	1.05 (0.13)
	Butanol	No DA	1.05 (0.15)	1.04 (0.22)

2d. Event-related potentials

Olfactory event-related brain potentials (OERPs) were recorded in response to a series of temporally distinct odor events that stimulated the olfactory nerve only, with varying degrees of intensity, and with minimal habituation.

Odor stimuli were presented to subjects via a dynamic multi-odorant air dilution olfactometer (OM4/B, Heinrich Burghart GmbH,Wedel, Germany). This apparatus allowed for precisely timed pulses of odorants to be embedded in a constantly flowing air stream with specified temperature and humidity (36.5 °C; 80% relative humidity) without transient pressure artifacts. A continuous air stream was delivered to one nasal chamber via a Teflon™ tube inserted approximately 1 cm into the naris. This was stream is then replaced by one of several odorized airstreams, using a non-electrical vacuum-switching device which allowed for switching airstreams without pressure, thermal, or humidity artifacts.

Three different concentrations of hydrogen sulfide (13.75 ppm, 8.25 ppm, 2.75 ppm) were randomly presented, with an inter-stimulus interval of approximately 20 seconds. The duration of each stimulus was 200 msec, with a rise time of less than 20 msec. Hydrogen sulfide was used because, unlike some other odorants, it is a relatively pure olfactory nerve stimulant that does not simultaneously stimulate the trigeminal nerve at the concentrations we employ. The 20-second interval between successive stimuli minimized effects of habituation.

The EEG was recorded from 36 locations across the scalp, and then corrected for eye-movements and other artifacts. OERPs were calculated by averaging the EEG recordings time-locked to olfactory events and were obtained separately for each subject during each session in response to each level of odorant intensity.

Two findings are described here. First, there were clear differences between the OERPs recorded from the PD and control subjects (Figures 1-3). Second, there was no apparent effect of drug treatment on the OERPs from PD subjects (Figure 4).

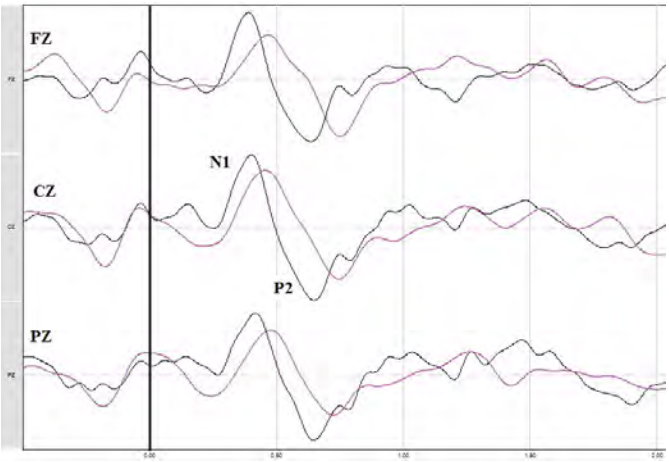

Figure 1 shows OERPs averaged across all of the control subjects. Each panel contains recordings from one of three midline electrode sites extending from the front (Fz) to the vertex (Cz) to the back of the head (Pz). The black and red lines show respectively responses to odorants of high and low concentrations. Time is shown at the bottom of the figure, and the onset of the odorant (time 0) is indicated by a vertical black line in each panel. Negative is represented as upward and positive as downward. The classic "N1" and "P2" of the OERP are labeled in the central panel.

Figure 1. Olfactory event-related potentials for control subjects

A similar pattern can be seen at all three electrode sites, which indicates that it was broadly distributed across the scalp. The magnitude of the response -- as measured by the peak (N1) to peak (P2) difference -- was similar for odorants of high and low concentrations. Concentration did, however, influence the latency of the OERP; N1 and P2 peaks occurred later in response to odorants with low than high concentrations.

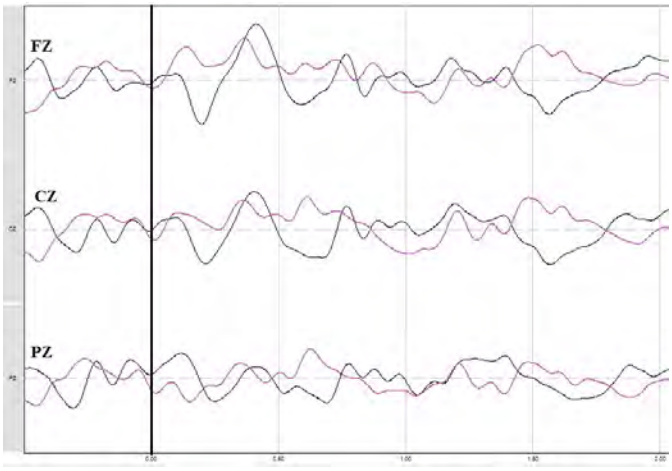

Figure 2 shows the OERPs averaged across all of the PD subjects. The format and scale of this figure are identical to those of Figure 1. A similar pattern can again be seen at all three electrode sites. This pattern, however, is rather different than that observed for the control subjects. The PD OERPs are flatter and display only minimal signs (shown more clearly in Fig. 3) of distinct N1 and P2 peaks and of systematic differences between responses to odors of different concentrations. It is worth noting that, with the possible exception of one subject, all of the PD subjects performed above chance on the behavioral tests of olfaction.

Figure 2. Olfactory event-related potentials for PD subjects

Unpublished data.

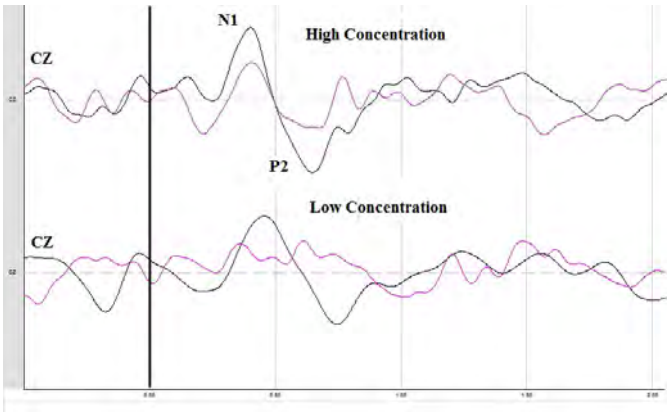

Figure 3. PD and control OERPs to strong and weak odorants

Figure 3 directly compares OERPs from control (black lines) and PD subjects (red lines) at the vertex (Cz). Responses to strong and weak odorants are shown respectively in the top and bottom panels. Format and scale are the same as in Figures 1 and 2. As can be seen, strong odorants did elicit an OERP, albeit a reduced one, in PD subjects. This diminished response is not equivalent to the OERPs to weak odorants elicited from control subjects. The former has the same latency but less amplitude as the control OERPs to strong odorants, while the latter has a longer latency but similar amplitude. The OERPs elicited from PD subjects by weak odorants were more-or-less flat lines.

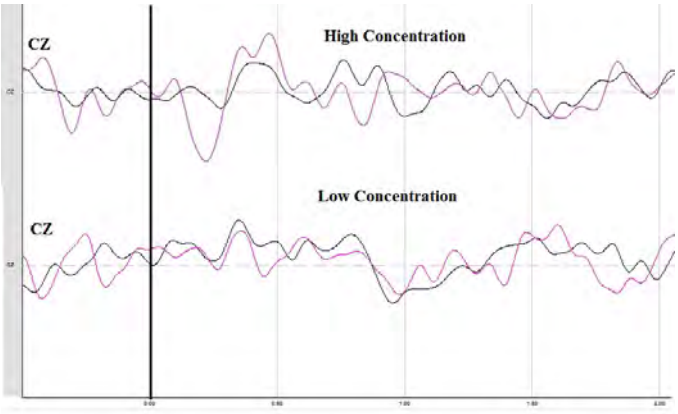

Figure 4. PD OERPs to strong and weak odorants before and during dopamine therapy

Finally, Figure 4 compares the OERPS elicited from the PD subjects prior to (black lines) and during (red lines) dopamine therapy. As can be seen, the OERPs elicited by strong odorants during the two sessions show little systematic difference (especially with regard to N1 and P2), while OERPs in response to weak odorants were essentially absent during both sessions.

3. Gustation

The project employs three tests - involving both the whole mouth and different sectors of the tongue - to examine the detection and identification of tastes, as well as the perception of their intensity and hedonic value. Below, we report results from the Regional Taste Identification Test which appears to be most sensitive to PD. The stimuli consisted of 25 microliters of single concentrations of sucrose, sodium chloride, citric acid, or caffeine, equated for physical viscosity by the addition of cellulose, presented via pipette to the front or the back of the tongue on the left or right side. After application at a stimulus site, the subject is asked to identify the resulting taste as sweet, salty, sour, or bitter and to rate its intensity verbally on a rating scale.

Table 5 presents overall accuracy (percent correct averaged across tongue sectors) in identifying each of the four tastes. Displayed are the means and standard deviations for the PD and control groups during the dopamine and non-dopamine sessions. The pattern shown here for gustation is similar to that shown above for olfaction (Tables 2 and 4). There was better performance by control than by PD subjects and no apparent influence of dopamine on the PD test scores.

Table 5: Comparison of taste measures between PD and control subjects. Values represent percent correct identification of total trials on entire tongue (24 trials per tastant; 96 trials per test session plus rinses). Controls did not receive dopamine.

Taste Measures	Session	PD (N=10) Mean (SD)	Control (N=6) Mean (SD)
Sucrose	No Dopamine	68 (20)	91 (11)
	Dopamine	59 (21)	96 (04)
NaCl	No Dopamine	60 (29)	79 (20)
	Dopamine	58 (32)	93 (02)
Citric acid	No Dopamine	50 (20)	53 (30)
	Dopamine	48 (25)	71 (29)
Caffine	No Dopamine	61 (30)	74 (28)
	Dopamine	49 (21)	67 (30)

4. Touch

4a. Semmes-Weinstein Point Tactile Thresholds

The median (range) threshold values of the monofilament single point threshold tests which employed seven staircase reversals on 10 locations of the body are shown for the no dopamine and dopamine PD test sessions and for the control subjects in Table 6a and b, respectively. It is apparent that considerable variability in the test scores was present in both the PD and control cohorts, and that PD and dopamine repletion has little effect on these tactile measures. These results must be viewed with caution, however, in light of the small sample sizes.

Table 6a: Median (Range) Monofilament Test Scores before Dopamine Repletion. Smller numbers indicate greater sensitivity.

NO DOPAMINE	Left Finger	Right Finger	Left Hand	Right Hand	Left Forearm	Right Forearm	Left Foot	Right Foot	Left Plantar Hallux	Right Plantar Hallux
PD (n = 10)	1.79 (2.30)	3.35 (7.15)	3.25 (4.75)	4.90 (9.80)	4.09 (7.00)	4.11 (5.45)	5.53 (34.67)	7.05 (47.58)	5.36 (134.48)	11.98 (132.78)
Controls (n = 6)	2.39 (5.89)	2.70 (4.75)	4.11 (4.03)	3.20 (4.95)	4.59 (21.30)	4.63 (8.90)	12.90 (24.53)	13.54 (25.08)	12.91 (31.12)	9.58 (16.76)

Table 6b: Median (Range) Monofilament Test Scores after Dopamine Repletion (PD group only) in Session 2. Controls were not given dopamine therapy. Smaller numbers indicate greater sensitivity.

DOPAMINE	Left Finger	Right Finger	Left Hand	Right Hand	Left Forearm	Right Forearm	Left Foot	Right Foot	Left Plantar Hallux	Right Plantar Hallux
PD (n = 8)	2.62 (2.30)	3.47 (2.88)	4.23 (4.05)	5.33 (8.54)	4.92 (8.50)	5.13 (8.75)	16.46 (25.86)	10.21 (46.52)	7.48 (79.76)	12.41 (132.44)
Controls (n = 3)	3.73 (0.35)	5.88 (7.03)	4.35 (6.18)	5.48 (4.58)	4.96 (13.06)	3.73 (19.65)	20.18 (22.35)	15.71 (22.15)	8.31 (21.00)	13.32 (132.44)

 Unpublished data.

Spearman test-retest correlation coefficients between the Session 1 and Session 2 test measures were computed for the above body locations. The thresholds for corresponding left and right locations were averaged, and PD and control subject data was combined to increase the sample size to 8. Although these measures must be conservatively viewed in light of the small sample sizes, it is noteworthy that the plantar hallux value was the most reliable (r = 0.72) and falls near the range observed in a much larger study of normal subjects performed for this project that assessed the reliability of different psychophysical approaches for determining point tactile thresholds (Tracey, Greene & Doty, 2011, submitted). The higher reliability coefficient may reflect the broader range of individual test scores of this measure.

4b. Spatial Tactile Sensation

JVP domes (Lafayette Instrument Co., Chicago, IL) were used to assess spatial tactile sensation. The test stimuli are small plastic pegs with hemispherical heads that measure 19 mm in diameter. The surface of the head is grated, with parallel grooves and ridges that are equal in width. There are 11 domes ranging in groove width from .35 mm to 4.0 mm. A staircase procedure was employed to determine a subject's ability to discern between the directions of the grooves in a same/different paradigm. In general, both the controls and the PD patients had significant difficulty with this task at all body locations, resulting in ceiling effects for all but two trials for all subjects. For this reason, we have changed the task recently so that a subject must now simply indicate the direction of the grooves relative to a body part on each trial. This minimizes the need to remember a prior stimulation and eliminates the possible influences from subtle variations of stimulus pressure between trials that could lead to a report of stimulus differences.

5. Auditory Tests

Each of the study participants underwent assessment with a battery of psychophysical and electrophysiological auditory tests. Current preliminary findings are described below. As previously shown in Table 1, demographics are comparable for the PD and health control subject groups. Therefore, neither age nor gender confounds the present analysis of auditory test data.

5a. Pure-tone hearing thresholds

The mean pure tone thresholds are shown for the left and right ear sides for the PD and control subjects in Table 7. Pure tone hearing threshold data were analyzed with reference to ANSI S3.6 (1996) guidelines [< 20 dB HL = normal hearing; 20-40 db HL = mild hearing loss; 40-60 db HL = moderate hearing loss; 60-70 dB HL = moderately severe hearing loss; 70-90 dB HL = severe hearing loss; > 90 dB HL = profound hearing loss]. For the PD and control subject groups, average hearing thresholds were within normal limits for from the low frequencies that we tested (250 to 2000 Hz). The mean pure tone thresholds were suggestive of a mild hearing loss at the higher frequencies for both subject groups, with greater losses in the PD subjects. At the 4000 Hz test frequency, hearing thresholds were decreased for the left versus the right ear in each group. It is of interest that there is a tendency for PD patients when on dopamine therapy to have higher thresholds (i.e., less sensitivity) than when not on dopamine therapy. More data are needed with the test orders equally counterbalanced before it will be possible to determine whether this is a true phenomenon.

Table 7: Mean and standard deviation for pure-tone auditory threshold values obtained for the left and right ears from PD and control participants.

	No Dopamine Left Ear Mean (SD)	No Dopamine Right Ear Mean (SD)	Dopamine Left Ear Mean (SD)	Dopamine Right Ear Mean (SD)
PD Subjects				
250 Hz	14.00 (5.16)	14.00 (5.16)	14.38 (4.17)	15.00 (6.55)
500 Hz	16.00 (6.58)	15.50 (6.85)	18.13 (5.94)	17.50 (8.45)
1000 Hz	13.00 (12.06)	16.00 (12.65)	17.50 (11.65)	18.13 (11.63)
2000 Hz	15.50 (8.64)	16.50 (7.47)	21.25 (8.76)	18.13 (7.04)
3000 Hz	27.50 (17.36)	27.00 (20.84)	30.63 (18.41)	30.63 (23.06)
4000 Hz	32.00 (18.14)	27.00 (21.76)	36.25 (18.47)	30.00 (22.83)
6000 Hz	38.50 (17.33)	33.50 (17.65)	38.75 (19.59)	35.63 (18.98)
8000 Hz	36.00 (19.41)	35.50 (16.41)	34.38 (19.17)	37.50 (19.64)
Control Subjects				
250 Hz	13.33 (6.06)	15.00 (6.32)	11.67 (7.64)	13.33 (5.78)
500 Hz	17.50 (7.58)	15.00 (6.32)	16.67 (11.55)	13.33 (10.41)
1000 Hz	15.00 (8.37)	15.83 (7.36)	15.00 (8.66)	15.00 (8.66)
2000 Hz	16.67 (8.76)	14.17 (4.92)	20.00 (10.00)	16.67 (5.78)
3000 Hz	25.83 (8.61)	18.33 (6.06)	31.67 (10.41)	20.00 (8.66)
4000 Hz	30.00 (12.65)	21.67 (9.31)	31.67 (16.07)	21.67 (10.41)
6000 HZ	30.00 17.89)	25.83 (9.70)	28.33 (27.54)	21.67 (16.07)
8000 Hz	36.67 (16.63)	38.33 (8.76)	33.33 (23.63)	36.67 (11.55)

5b. Tests of central auditory processing

Five auditory tests designed to identify and quantify central auditory processing deficits were administered. In the *Filtered Words* test, the subject is asked to repeat words that are sound muffled. The stimuli consist of one-syllable words that have been low-pass filtered at 500 Hz. Two practice words and 20 test words are presented to each ear. The filtered words test evaluates perception of distorted speech or speech compromised by a poor acoustic environment. In the *Auditory Figure-Ground* test, the ability to understand words in the presence of background noise is assessed. One syllable words are recorded in the presence of multi-talker speech babble noise at the 0 dB signal-to-noise (S/N) ratio. Two practice words and 20 test words are presented to each ear. In the dichotic *Competing Words* test, the subject hears two words simultaneously, one in the right ear and one in the left ear. Two practice word pairs precede the presentation of 15 non-practice word pairs. The subject is instructed to repeat the words presented in each ear, repeating the word heard in the right ear first. Then, a second set of 2 practice word pairs and 15 word pairs are presented, with the subject repeating the word heard in the left ear first. In the *Competing Sentences* test, pairs of sentences unrelated in topic are presented to the right and left ears. The sentence pairs have simultaneous onset and offset times. This test consists of a directed listening task, in which the subject is instructed to direct attention to the stimuli presented in one ear, while ignoring stimuli presented to the other ear. Two practice sentence pairs followed by 10

test sentence pairs are initially presented. The subject is instructed to repeat only the sentence heard in the right ear. A similar set of practice and test sentence pairs is then presented with the subject being instructed to repeat only the sentence heard in the left ear.

The results of five tests of central auditory processing are shown in Tables 8a and 8b. Mean scores (percentiles based on standard scores) were essentially the same for the PD and control subjects for two of the tests (Filtered Words Test and Competing Sentences Test). For the other two tests (Auditory Figure Ground and Competing Words Test), mean scores from both dopamine and non-dopamine test sessions appeared to be lower (poorer) for the PD group versus the control group. Moreover, as was seen for pure-tone thresholds, the test scores were nominally lower during the dopamine than during the non-dopamine test sessions. Given the limited number of subjects in each group at this time, this trend must be viewed with caution. We will continue to closely analyze data for these central auditory processing measures.

Table 8a: Scores on four auditory tests designed to measure central auditory processing in the no dopamine therapy session.

Test Measure	PD Subjects Mean (SD)	Controls Mean (SD)
Filtered Words Test	32.80 (4.13)	32.50 (2.17)
Auditory Figure Ground	27.50 (8.21)	29.33 (4.76)
Competing Words Test	47.10 (7.88)	49.17 (4.26)
Competing Sentences Test	19.90 (0.32)	19.50 (0.84)

Table 8b: Scores on four auditory tests designed to measure central auditory processing in the dopamine therapy session. Controls did not receive dopamine.

Test Measure	PD Subjects Mean (SD)	Controls Mean (SD)
Filtered Words Test	31.75 (4.56)	35.33 (1.53)
Auditory Figure Ground	26.50 (7.54)	31.67 (5.03)
Competing Words Test	45.50 (6.89)	51.33 (2.08)
Competing Sentences Test	19.75 (0.71)	19.67 (0.58)

The Hearing in Noise Test (HINT) measures sentence speech reception thresholds (sSRTs). The HINT is a reliable and efficient clinical research method for directly assessing speech perception in quiet and noisy conditions. Findings are displayed in Table 9. There were no differences between PD and control subjects in HINT scores for any noise condition or from Session 1 (no dopamine) to Session 2 (dopamine repletion in PD patients).

Table 9: Hearing in Noise Test (HINT) values for left and right ears for PD patients and controls. No dopamine refers to dopamine test session; controls did not receive dopamine.

Hearing in Noise Test (HINT)	Left Ear No Dopamine Mean (SD)	Right Ear No Dopamine Mean (SD)	Left Ear Dopamine Mean (SD)	Right Ear Dopamine Mean (SD)
PD				
Quiet	1.00 (0.00)	1.00 (0.01)	1.00 (0.00)	1.00 (0.00)
+5	0.98 (0.03)	0.98 (0.04)	0.94 (0.10)	0.96 (0.04)
0	0.78 (0.22)	0.84 (0.14)	0.77 (0.12)	0.81 (0.12)
-5	0.25 (0.11)	0.25 (0.20)	0.27 (0.16)	0.24 (0.20)
Controls				
Quiet	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)
+5	0.99 (0.02)	1.00 (0.00)	0.99 (0.01)	1.00 (0.00)
0	0.82 (0.14)	0.91 (0.12)	0.91 (0.06)	0.87 (0.09)
-5	0.27 (0.18)	0.28 (0.07)	0.31 (0.11)	0.36 (0.14)

Assessment of Auditory Temporal Resolution

Temporal processing was assessed using the Gaps in Noise (GIN) test at a stimulus intensity level of 50 dB HL. Results of this well-validated clinical test are relatively independent of peripheral hearing loss. The GIN test places minimal cognitive demand on subjects. The mean (SD) values for the left and right ears, as well as the combined left and right ear data, are presented in Table 10. There are no clear and consistent differences between PD versus control subjects in either Session 1 or 2.

Table 10: Percent correct score values for the Gaps in Noise (GIN) test. Controls in far right column are for the PD dopamine sessions but did not receive dopamine.

Ear	PD Subjects No Dopamine Mean (SD)	HC Subjects No Dopamine Mean (SD)	PD Subjects Dopamine Mean (SD)	HC Subjects No Dopamine Mean (SD)
Left	51.50 (17.04)	50.30 (16.93)	48.50 (19.99)	53.67 (9.02)
Right	53.90 (14.94)	56.83 (12.45)	52.50 (14.81)	59.33 (10.97)

5c. Auditory brainstem responses

The auditory brainstem response (ABR) latencies and amplitudes for waves I – V and inter-peak latencies (IPLs) I-III, I-V and III-V are presented in Tables 11a and 11b. There were no differences in mean absolute or relative (inter-peak) latency values between the two groups in the non-dopamine or dopamine test sessions. These observations are tentative, however, until more data are collected.

Table 11a: Brainstem EP latencies and amplitudes for non-dopamine test sessions.

Brainstem AEP	PD Left Mean (SD)	PD Right Mean (SD)	Control Left Mean (SD)	Control Right Mean (SD)
Latencies (msec)				
I	1.84 (0.11)	1.80 (0.10)	1.74 (0.20)	1.81 (0.16)
II	3.04 (0.14)	3.07 (0.17)	2.94 (0.13)	2.98 (0.13)
III	4.03 (0.13)	4.06 (0.09)	3.99 (0.18)	4.00 (0.19)
IV	5.35 (0.17)	5.37 (0.15)	5.22 (0.23)	5.32 (0.21)
V	5.90 (0.17)	5.92 (0.22)	5.90 (0.26)	5.89 (0.31)
I-III	2.19 (0.16)	2.25 (0.12)	2.25 (0.25)	2.20 (0.24)
I-V	4.06 (0.23)	4.12 (0.26)	4.15 (0.33)	4.08 (0.35)
III-V	1.87 (0.18)	1.87 (0.18)	1.91 (0.13)	1.89 (0.14)
Amplitudes (µV)				
I	0.17 (0.05)	0.20 (0.09)	0.20 (0.08)	0.23 (0.09)
III	0.17 (0.10)	0.21 (0.10)	0.20 (0.03)	0.21 (0.03)
V	0.40 (0.15)	0.43 (0.21)	0.36 (0.10)	0.43 (0.10)
V/I ratio	2.48 (0.96)	2.22 (0.131)	2.18 (1.09)	2.23 (1.16)

Table 11b: Mean (SD) brainstem EP latencies and amplitudes for dopamine test sessions.

Brainstem AEP	PD Left Mean (SD)	PD Right Mean (SD)	HC Left Mean (SD)	HC Right Mean (SD)
Latencies (msec)				
I	1.81 (0.10)	1.79 (0.10)	1.56 (0.10)	1.53 (0.10)
II	3.10 (0.14)	3.04 (0.12)	2.99 (0.22)	2.93 (0.18)
III	4.03 (0.12)	4.03 (0.09)	3.97 (0.19)	4.03 (0.25)
IV	5.32 (0.09)	5.31 (0.18)	5.28 (0.29)	5.26 (0.44)
V	5.84 (0.09)	5.88 (0.23)	5.91 (0.38)	5.87 (0.50)
I-III	2.22 (0.15)	2.24 (0.12)	2.41 (0.25)	2.50 (0.33)
I-V	4.03 (0.19)	4.10 (0.24)	4.35 (0.43)	4.33 (0.57)
III-V	1.81 (0.17)	1.86 (0.24)	1.94 (0.19)	1.84 (0.26)
Amplitudes (µV)				
I	0.16 (0.05)	0.19 (0.10)	0.23 (0.12)	0.23 (0.07)
III	0.17 (0.06)	0.19 (0.07)	0.20 (0.08)	0.15 (0.06)
V	0.38 (0.15)	0.36 (0.15)	0.42 (0.14)	0.35 (0.18)
V/I ratio	2.47 (0.88)	1.96 (0.39)	2.37 (1.72)	1.67 (1.06)

5d. Auditory cortical evoked responses

The latency of the auditory late response P1 component was slightly longer (~ 4 to 7 ms) for the PD versus control group in both test sessions. No clear latency differences were apparent for other major wave components of the auditory late response (e.g., N1, P2, or P3). These findings are preliminary and

necessarily tentative. We'll continue to closely analyze latency and amplitude data for auditory cortical evoked response recordings. Findings will be further described in future progress reports.

6. Vision

A battery of state-of-the-art visual tests was administered to each study participant. Following a brief eye examination, visual acuity and contrast sensitivity was measured using standardized ETDRS and Low-Contrast Sloan letter charts. Color vision was tested using the L'Anthony D-15 Desaturated (D-15DS) Color Test. Optical coherence tomography (OCT) was then performed on each eye, utilizing Zeiss Stratus and Cirrus machines as well as the Heidelberg Spectralis system. This brief test scans the back of the eye in order to measure the retinal nerve fiber layer thickness and macular thickness and volume. Next, visual evoked response (VER) testing was performed, which measures electrical potentials generated along the optic nerve and into the brain. Finally, pattern electroretinography (PERG) was performed. This test evaluates neuronal and ganglion cell activity in the inner retina by measuring electrical potentials generated at the surface of the eye by flashing patterns presented to the retina.

At this point in the study several trends seem to be emerging. There appears to be a significant difference in low-contrast visual acuity (Table 12), with the PD subjects able to read approximately one line less than the control subjects on both the 2.5% and 1.25% contrast charts.

Table 12: Selected vision measures for PD and Control subjects

Vision Measures	PD cases (N=10) Session 1 (19 eyes)	PD cases (N=8) Session 2 (15 eyes)	Control (N=6) Session 1 (12 eyes)	Control (N=3) Session 2 (6 eyes)
Visual Acuity (Snellen equivalent)	**Median (range)**			
	20/20 (20/40-20/16)	20/20 (20/32-20/16)	20/20 (20/25-20/12.5)	20/20 (20/25-20/12.5)
Low-Contrast Acuity (Sloan charts)	**Median (range)**			
2.5%	28 (7-40)	25 (11-37)	32 (18-38)	29 (16-37)
1.25%	16 (0-33)	12 (0-29)	21 (12-28)	17 (3-25)

Data presented in our earlier progress report suggested a difference in average RNFL thickness between the two study groups, but at this stage this difference seems smaller as more subjects have been tested and the two groups are more closely matched in age. On the Stratus OCT machine, the mean RNFL thickness for PD eyes without dopamine therapy is now 97.67 micrometers (μm) as compared to 98.37 μm in healthy controls, while on Cirrus OCT these values were 89.8 μm in PD eyes vs. 94.0 μm in healthy controls. The measurements on the Spectralis OCT machine were very similar to Cirrus: 92.84 μm in PD eyes vs. 96.90 μm in healthy controls.

One possible explanation for the difference in results between systems is that only 8 control eyes were scanned on the Stratus machine vs. 15 PD eyes, while on the Cirrus and Spectralis systems the numbers were larger: 12 and 10 control eyes vs. 19 PD eyes. The Cirrus and Spectralis systems are more modern high-resolution spectral domain machines, and the reliability and consistency of results between scan sessions is greater. The results on Cirrus and Spectralis, then, probably better reflect the total study population as a whole.

Another important measurement obtained by OCT is that of total macular volume (Table 13). Thus far we have found no difference between the PD and control subjects on this measure (Stratus: 6.61 mm^3 vs. 6.58 mm^3; Cirrus: 9.9 mm^3 vs. 10.1 mm^3).

*Table 13: Selected OCT measures for PD and control subjects. *Indicates control for PD dopamine sessions; Controls received no dopamine therapy.*

OCT Measures	**PD** (N=10) Dopamine	**PD** (N=8) Non-Dopamine	**Control** (N=6) Dopamine*	**Control** (N=3) Non-Dopamine
Stratus OCT				
RNFL thickness (μm), Mean (SD)	97.67 (9.13) (15 eyes)	93.68 (5.66) (12 eyes)	98.37 (9.20) (8 eyes)	100.33 (8.88) (6 eyes)
Total macular volume (mm^3), Mean (SD)	6.61 (0.21) (13 eyes)	6.52 (0.19) (12 eyes)	6.58 (0.18) (10 eyes)	6.55 (0.10) (6 eyes)
Cirrus OCT				
RNFL thickness (μm), Mean (SD)	89.8 (9.36) (19 eyes)	88.8 (10.27) (14 eyes)	94.0 (8.28) (12 eyes)	93.0 (8.85) (6 eyes)
Total macular volume (mm^3), Mean (SD)	9.9 (0.22) (19 eyes)	9.9 (0.27) (13 eyes)	10.1 (0.45) (12 eyes)	9.9 (0.14) (6 eyes)
Spectralis OCT				
RNFL thickness (μm), Mean (SD)	92.84 (10.79) (19 eyes)	91.54 (9.83) (13 eyes)	96.90 (8.86) (10 eyes)	97.17 (10.01) (6 eyes)
Total macular volume (mm^3), Mean (SD)	8.26 (0.32) (19 eyes)	8.20 (0.34) (13 eyes)	8.41 (0.40) (12 eyes)	8.20 (0.20) (6 eyes)

Results of color vision testing reveal an interesting difference between the PD and control subjects, with 40% of PD subjects having abnormal results at Session 1 compared to 33% among the controls. subjects. However, there is almost no difference between the PD and control subjects in Total Error Score, Selectivity Index, and Confusion Index (Table 14), so it may be too early to conclude that any PD-related deficit in color vision has been demonstrated.

Table 14: Selected L'Anthony D-15 Desaturated (D-15DS) Color Test Results, Moment of Inertia analysis method

D-15DS Measures	PD cases (N=10) Session 1	PD cases (N=8) Session 2	Control (N=6) Session 1	Control (N=3) Session 2
Total Error Score, mean (SD)	9.11 (2.53)	9.13 (3.06)	9.23 (3.01)	9.87 (3.26)
Selectivity Index, mean (SD)	1.75 (0.27)	1.68 (0.37)	1.85 (0.53)	1.45 (0.19)
Confusion Index, mean (SD)	1.54 (0.47)	1.51 (0.51)	1.58 (0.61)	1.57 (0.50)
Interpreted as abnormal, Percentage of total (number)	40% (4/10)	37.5% (3/8)	33.3% (2/6)	33.3% (1/3)

Unpublished data.

Results of the pattern visually-evoked potential (PVEP) recordings thus far demonstrate a trend toward increased latency in PD subjects compared to the controls, and a significant decrease in amplitude (Table 15). For the 32x32 check size, mean latency was 106.70 ms and 101.85 ms, respectively (upper limit of normal being approximately 118 ms), while mean amplitude was 4.17 μV vs. 8.56 μV. The differences were imilar for all check sizes (8x8, 16x16, 32x32 and 64x64).

Table 15: Pattern visual evoked potential- mean and standard deviations for p100 amplitudes and latencies for different check size. No controls received dopamine therapy but are controls for the PD dopamine therapy periods.

Pattern VEP

8x8

	No Dopamine				**Dopamine**			
	Amplitude		**Latency**		**Amplitude**		**Latency**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients	4.55	3.19	110.08	9.55	4.04	2.70	110.54	11.54
Controls	7.40	2.99	107	13.21	7.17	1.82	96.42	4.10

16x16

	No Dopamine				**Dopamine**			
	Amplitude		**Latency**		**Amplitude**		**Latency**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients	4.38	2.21	106.73	11.11	4.10	2.79	108.64	12.40
Controls	8.52	3.64	101.45	10.10	8.23	2.74	96.92	3.35

32x32

	No Dopamine				**Dopamine**			
	Amplitude		**Latency**		**Amplitude**		**Latency**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients	4.17	2.40	106.70	9.60	3.91	3.04	109.96	10.76
Controls	8.56	2.75	101.85	10.53	7.10	1.81	95.00	4.38

64x64

	No Dopamine				**Dopamine**			
	Amplitude		**Latency**		**Amplitude**		**Latency**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients	3.65	1.88	116.70	15.90	3.63	3.87	110.50	11.68
Controls	8.82	3.19	107.60	12.35	7.20	2.71	101.17	2.64

The pattern electroretinography (PERG) data are presented in Table 16. Thus far there appears to be a trend toward reduced amplitudes at P50 (1.40 μV vs. 2.45 μV) and N95 (2.57 μV vs. 3.84 μV) in the PD cohort vs. the controls.

Table 16: Pattern electroretinography - mean (SD) for power amplitudes and latencies of positive and negative peak. Controls under Dopamine Session do not receive dopamine.

Pattern ERG

P50

	Non-Dopamine Session				**Dopamine Session**			
	Amplitude		**Latency**		**Amplitude**		**Latency**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients	1.40	0.87	51.97	7.31	1.32	0.84	44.71	2.97
Controls	2.45	1.42	52.35	7.59	2.30	1.70	52.33	5.88

N95

	Non-Dopamine Session				**Dopamine Session**			
	Amplitude		**Latency**		**Amplitude**		**Latency**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients	2.57	1.06	92.89	16.85	2.64	1.32	96.54	19.49
Controls	3.84	2.21	106.25	5.29	3.55	1.77	95.42	16.30

Comparisons of vision measures during the dopamine and non-dopamine sessions show no clear trends so far. Performances on all tests are similar between sessions, for both PD and control subjects, and any differences between patients and controls are similar and consistent for both sessions. Given the smaller number of subjects having completed the PD dopamine session, particularly among the controls, it may simply be too early for any trends to emerge.

7. Balance

We employed Computerized Dynamic Posturography (CDP) to assess each subject's ability to quickly and automatically restore balance (long-loop postural reflex) in response to sudden unexpected perturbations of a platform beneath their right or left foot. Table 17 displays mean (SD) reaction times to make such postural adjustments in response to a series of medium (MFL) and large (LFL) forward translations (scaled to the subject's height) of the platforms.

As can be seen from the table, the mean latency to begin postural adjustment is similar for the control and PD subjects tested so far. Likewise, no influence of dopamine repletion is yet apparent.

In light of the important role played by the vestibular system in motor control, a function well-known to be influenced by PD, we recently expanded our vestibular test battery. Each of three new tests uses eye-movements to evaluate the integrity of the peripheral vestibular system. One examines saccades to briefly presented visual targets, and another examines continuous smooth-pursuit movements to track a moving target. The third test uses caloric stimulation to elicit the vestibular-ocular reflex. A clinical evaluation of the results has so far detected no abnormalities or any difference between the two test sessions for any subject. But, given the small number of subjects tested with these new tests (3 PD and 1 control in non-dopamine sessions and two PD in dopamine sessions), it is much too early to reach any conclusions.

Table 17: Mean (SD) reaction times (msec) during Computerized Dynamic Posturography (CDP) for PD and Control subjects. MFL= Medium forward latency; LFL= Large forward latency.

Leg	Stimulus	Session	PD (N=9) Mean (SD)	Controls (N=6) Mean (SD)
Left	MFL	No Dopamine	128.89 (11.00)	135.00 (15.00)
		Dopamine	132.86 (8.81)	130.00 (0.00)
	LFL	No Dopamine	125.56 (9.56)	131.67 (10.67)
		Dopamine	128.57 (9.90)	130.00 (8.36)
Right	MFL	No Dopamine	126.67 (8.16)	131.67 (10.67)
		Dopamine	127.14 (10.30)	133.33 (9.43)
	LFL	No Dopamine	124.44 (8.31)	128.33 (10.67)
		Dopamine	122.86 (10.30)	133.33 (9.43)

8. TRODAT Technetium-99m SPECT brain imaging

We have found, as would be expected, significantly decreased uptake of the TRODAT tracer in the PD patients' brain regions rich in dopamine transporters when compared to that brains of the healthy controls. Since the inception of this program, 16 subjects (10 PD; 6 controls) have undergone TRODAT Tc-99m SPECT/CT brain imaging; 8 PD patients underwent a subsequent SPECT study (on vs. off pro-dopaminergic therapy), 3 of the 6 Control volunteers have undergone a subsequent SPECT study. Thus, a total of 27 TRODAT Tc-99m SPECT imaging studies have been performed so far.

For each study, 20.0 +/- 2 mCi of TRODAT Tc-99m was intravenously administered. Approximately 3 hours later, SPECT/CT brain imaging was performed using a Siemens Symbia ™ SPECT/CT with ultra-high resolution collimators. Immediately following acquisition of the SPECT functional images, a low dose CT of the brain was also obtained for anatomic localization and attenuation correction.

In keeping with previously published TRODAT imaging analysis, average counts per mm^3 were obtained for seven regions of interest (ROI): 1. Right Caudate Nucleus (RC); 2. Left Caudate Nucleus (LC); 3. Right Anterior Putamen (RAP); 4. Left Anterior Putamen (LAP); 5. Right Posterior Putamen (RPP); 6. Left Posterior Putamen (LPP) and a cortical background value (Right Superior Parietal Lobule (RSPL). Mean distribution volume ratios (DVR's) were then calculated for each striatum ROI relative to cortical background using the following formula : DVR= (ROI−Reference Region)/Reference Region.

Figure 5 displays representative transaxial images from all 27 TRODAT imaging experiments performed to this point -- 16 from non-dopamine and 11 from dopamine sessions. The left image within each pair shows the CT slice used to determine ROI's as well as the superimposed ROI's. The right image shows the fused TRODAT SPECT/CT on the identical transaxial slice, again with the six ROI's drawn. Bright colors indicate a higher DVR, i.e., more dopamine.

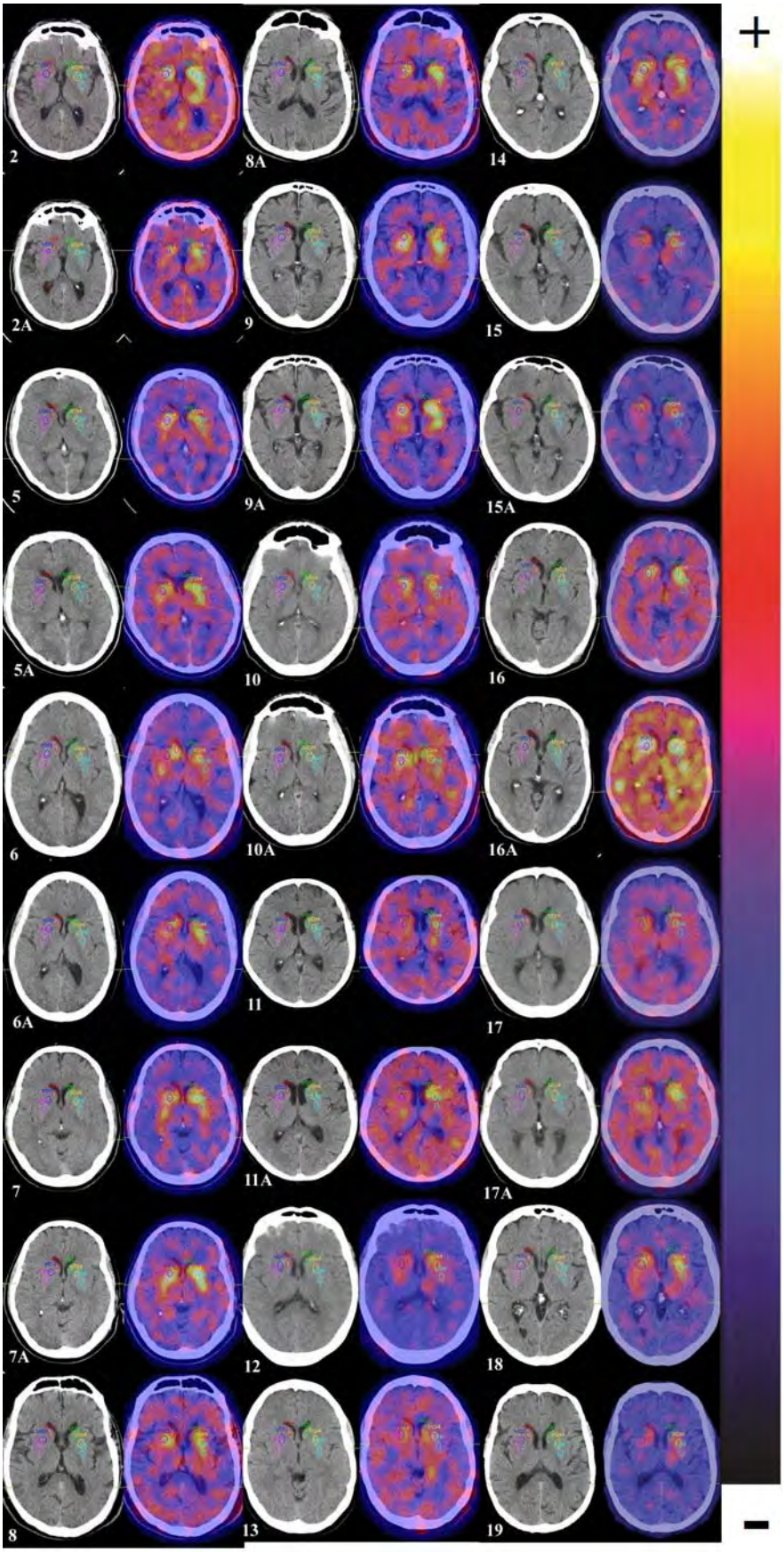

Figure 5. Axial images of CT and SPECT scans for all individual subjects during dopamine and non-dopamine sessions.

Unpublished data.

Table 18 summarizes the results of the imaging TRODAT analysis comparing OFF medication PD subjects and the initial control (C) study for the six Regions of Interest (ROIs).

Table 18: Group (control and PD) DVR values for each ROI during Session 1.

	C (Mean)	C (SD)	PD (Mean)	PD (SD)	P Value
R Caudate	0.7789	0.4059	0.3937	0.2965	0.0227
L Caudate	0.6192	0.3372	0.3315	0.2084	0.0258
R Ant Putamen	1.0515	0.3092	0.7129	0.3036	0.0250
L Ant Putamen	1.0428	0.4291	0.7860	0.2348	0.0701
R Post Putamen	0.8958	0.1589	0.3823	0.3091	0.0011
L Post Putamen	0.6721	0.2357	0.3510	0.3294	0.0283

Figure 6 depicts data from Table 18, graphically illustrating dopamine transporter depression in Parkinson's participants. The Y axis is DVR (ratio of counts per volume, therefore no units) and the X axis represents each of the 6 neuroanatomical locations. Error bars are standard deviations.

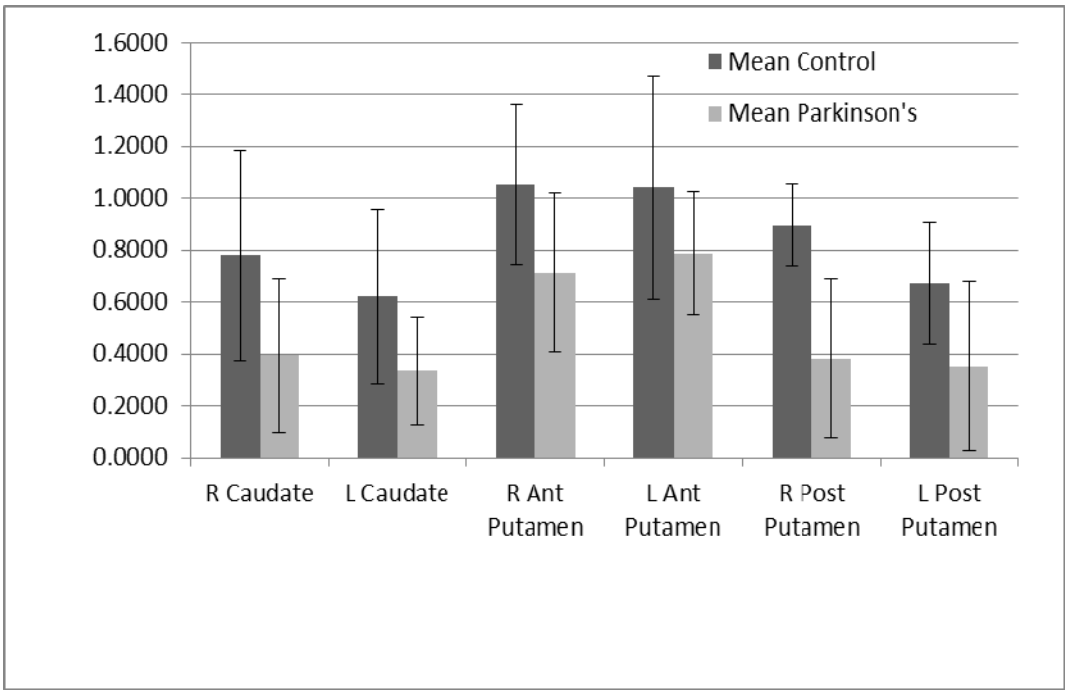

Figure 6. Group (control and unmedicated PD) DVR values for each ROI

9. Integration of Sensory and Imaging Measures for Predictive Power

This study assesses the influence of early Parkinson's disease on all major sensory systems, as well as on striatal dopamine levels, in the same subject cohort. As such, it provides a rare and valuable opportunity to examine the relationships between these measures and to appraise their relative sensitivity – alone and in combination – in discriminating between patients with early PD and healthy controls. The project has now

reached the stage of subject accrual at which we can begin to assess such effects.

Receiver Operating Characteristic (ROC) curves and C-statistics for several sensory measures and for an integrated measure (described below) of dopamine transporter level are presented in Figure 7. A single measure has been selected from each of the three sensory modalities that appears so far to be the most sensitivity to PD. The measures chosen for this preliminary assessment were the University of Pennsylvania Smell Identification Test (UPSIT), the Taste Quadrant Test, and our test of low contrast (2.5%) visual acuity. The ROC curves and C-statistics are used below to evaluate how well these measures – alone and in combination – discriminate between the 10 PD subjects during the session without dopamine repletion and the six control subjects during their first test session.

ROC curves display a measure's sensitivity (here the probability of a PD subject's score falling below a criterion value) against its specificity (here the probability of a control subject's score falling above the criterion) over a range of criterion values. Typically, sensitivity is plotted against 1 – specificity (here the probability of a control subject's score falling below the criterion). The resulting ROC curve will fall on a line of slope 1 if the measure discriminates at a chance level between PD and controls. If the measure discriminates above chance, the ROC curve will "bow" upwards from the line. The C-statistic equals the area under the ROC curve. It equals 0.5 when the ROC curve falls on the line, increases as discrimination becomes more sensitive, and reaches 1.0 when it is perfect.

The ROC curves presented in Figure 7 were obtained using a LOWESS method to fit a smooth curve through individual criterion data points. The diagonal in each panel corresponds to the line of slope 1 (chance discrimination). The left-most panel contains ROC curves for each of the three sensory measures. The visual measure (green) was the least sensitive (C-statistic = 0.59), the gustatory measure (red) was the next most sensitive (C-statistic = 0.78), and the olfactory measure (blue) was the most sensitive (C-statistic = 0.92).

The middle panel shows the ROC curve for the SPECT imaging measure. It was calculated for each for each subject by averaging their DVR across the six ROIs (see Section 8) and converting the average to a z-score (based on the mean and SD of the control subjects). As expected, the measure was quite sensitive at discriminating between PD and control subjects (C-statistic = 0.9), but not quite as sensitive as the UPSIT. Of course, the single integrated SPECT measure employed here may not be the most optimal one.

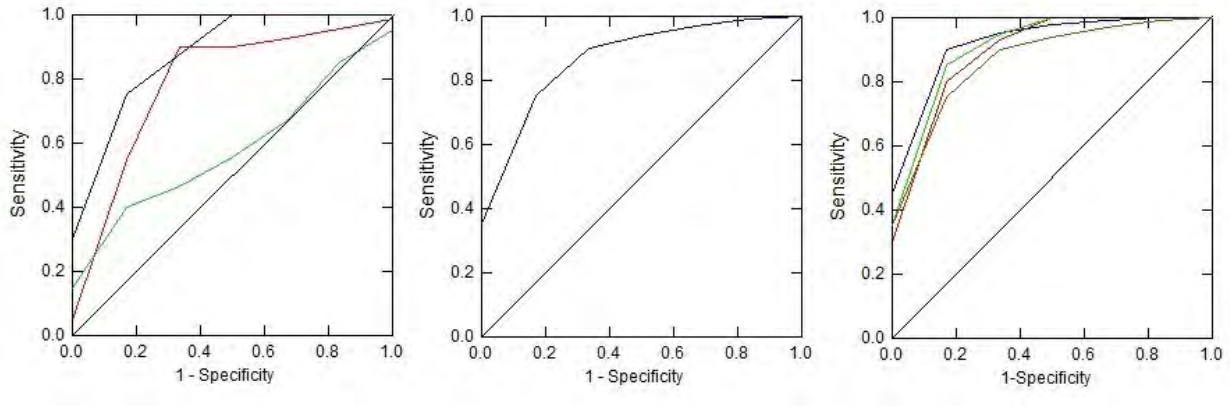

Figure 7. Receiver Operating Curves (ROC). Left panel shows visual (green), gustatory (brown), and olfactory (blue) measures individually, the middle panel the SPECT-TRODAT measure, and the right panel SPECT (brown) and combinations involving SPECT + olfaction + vision (red), SPECT + olfaction + gustation (green), and the combination of all four measures (blue). See text for details.

Measures were combined after being converted to z-scores (mean and SD based on control subjects' measurements). The combinations were weighted averages of the z-scores, with the contribution of each measure weighted by its individual C-statistic (minus 0.5). The only combination of two measures that performed better than either alone was gustation + vision (C-statistic = 0.83). A number of combinations involving three or more measures, however, were better discriminators than any of their constituents.

The ROC curves from these latter combinations are shown in the right-most panel of the figure. For purposes of comparison, the ROC curve (brown) is again presented for the SPECT measure alone. As can be seen, it is the least sensitive discriminator. The combination involving SPECT + olfaction + vision (red) was the next most sensitive (C-statistic = 0.93), and the combination involving SPECT + olfaction + gustation (green) was yet more sensitive (C-statistic = 0.95). The most sensitive combination was that involving all four measures (blue, C-statistic = 0.97).

The reliability of the C-statistics and their confidence intervals will be obtained using a set of procedures (ROCKIT) that employ maximum likelihood and jack-knifing to estimate parameter values and sampling distributions. ROC curves and C-statistics will be calculated for multiple measures within the same logistic regression model. As the number of tested subjects continues to increase, we will begin to examine also the correlations between multiple measures within and across sensory modalities. This will enable us to evaluate the level of discrimination provided by components or factors of shared variance across measures, as well as to combine measures in a more optimal and principled manner.

KEY RESEARCH ACCOMPLISHMENTS

- Added new vestibular measures to better assess PD influences on balance
- Increased subject accrual
- Initiated new counterbalancing paradigm
- Developed new Receiver Operating Characteristic algorithms
- Further validated the utility of TRODAT in differentiating motor neuron-related disorders

REPORTABLE OUTCOMES

The following journal articles and book chapters by the investigators have been published or accepted for publication since the start of the project. They either relate directly to Parkinsonism, to sensory dysfunction in neurodegenerative disease, or have benefited significantly from DOD support of the project.

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CONCLUSION

It is becoming apparent that PD is much more than a disease of the motor system. This research focuses on the sensory changes present in early PD that not only, in many cases, are disabling to PD patients, but may provide insight into the early elements of the disorder. Such insight could provide a substrate for mitigating disease progression through genetic or medical therapies. Importantly, understanding these changes and the way in which dopamine therapy may alter their expression may have direct benefit to patients. The present research may aid in the development of unique sensory biomarkers for early detection of PD.

Important findings are beginning to emerge in this study as subject accrual increases. It is becoming apparent that the function of only some sensory systems is markedly influenced by PD, although data based upon additional testing of more subjects is needed before definitive statements regarding the relative influences of PD and dopamine repletion therapy can be made.

 Unpublished data.