

**An Investigation
of the
Auditory Brainstem Response (ABR) Characteristics
of
People with Parkinson's Disease**

by

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Abstract

This paper documents the findings of research undertaken between 2000 and 2004. The subject of the research was the auditory brainstem response (ABR) characteristics of people with Parkinson's Disease (PD). The objective was to determine the potential efficacy of ABR as a technique for detecting the presence of PD and the performance of medication.

Autopsy is currently considered to be a gold standard in PD diagnostics, although modern medical imaging techniques, such as FDopa/FDG PET, are gaining acceptance as a reliable indicator. The problem with medical imaging techniques is that they represent a high capital cost method of evaluation which is not amenable to use, on a frequent basis, in clinical or pharmaceutical practice to assess disease progression or medication effectiveness. The application of a low cost tool, on the other hand, would potentially lend itself to both diagnostic and disease progression monitoring techniques and potentially provide a better means of medication regulation.

This research was concerned with the evaluation of several ABR parameters, specifically, the amplitudes and latencies of Waves III and V. Detailed tests were carried out on two groups of participants – a PD group and a control group. The ABR parameters of mildly-afflicted PD participants were assessed as a function of diurnal factors; medication level and mobility, and were compared against results from the control group. The results were subjected to statistical analysis, specifically ANOVA, Student's t-test and permutation analysis. The statistical results indicated that the amplitude of Wave III of the ABR was sensitive to the presence of PD and to variations in medication level. The amplitude of Wave V of the ABR was sensitive to variations in medication level. The latencies of Waves III and V were not sensitive to the presence of PD or medication levels.

Key Words

Parkinson's Disease

Auditory Brainstem Response (ABR)

Brainstem Auditory Evoked Response (BAER)

1. Introduction

1.1 Background and Impetus

The objective of this research was to conduct a detailed investigation of the auditory brainstem response (the so-called ABR, also referred to as the brainstem auditory evoked response or BAER) of people with Parkinson's Disease (PD), and to compare this with the ABR of people with no history of neurological disorders. More specifically, the purpose was to determine whether the ABR of humans had the potential to be used as the basis of a diagnostic tool for PD. A secondary objective was to determine whether such a diagnostic tool also had the potential for providing an objective measure of medication performance, with the possibility of improving the medication regime of PD patients. It needs to be stated from the outset, however, that it was not the intention of this research to determine the physiological genesis for any relationship that may exist between the ABR and the presence/absence of Parkinson's symptoms but, rather, to record the phenomena and present it as a basis for further investigation at a neuroscientific level.

The concept for the experimental work in this study was relatively straightforward. A group of people that had been diagnosed (by their neurologists) as having PD was used as the basis of experimentation and compared against a control group. ABR testing was carried out on both groups through a series of experiments that were designed to highlight differences between:

- Unmedicated PD participants and the control group
- Medicated PD participants and unmedicated participants
- Medicated PD participants as a function of diurnal factors.

At the time this research program commenced, the only broadly accepted, definitive tests for PD were based upon autopsy, or through the application of fluorodopa (F-Dopa) or flurodeoxyglucose (FDG)-based positron emission tomography (PET). Jankovic (1992) reported that one of the gold standards for the diagnosis of PD was considered to be the pathological finding of specific degeneration of nigral and other pigmented brain stem nuclei. However, research in the field by Brooks (1997) and

Stoessl and Ruth (1998) also highlighted the use of single photon emission tomography (SPECT) in terms of its use in detecting changes in brain metabolism and receptor binding. Frey *et al.* (1996) also observed that the binding to vesicular monoamine transporters and postsynaptic dopamine and other receptors (Schwarz *et al.* (1994); Kawabata *et al.* (1997) and Pirker *et al.* (1997)) in PD could also be measured using PET and SPECT.

Autopsy was, self-evidently, of no value to living patients, and the other imaging techniques were high in capital cost, thereby making them impractical for clinicians to use on a regular basis. The common techniques that were employed for diagnosis were therefore based upon clinical observations (often employing a number of broadly accepted “mobility” tests), followed by a subjective assessment of PD medication performance. In other words, those who were clinically suspected of having PD were treated with PD medication and their responses observed. Those that responded well to the medication were presumed to have a high probability of actually having the disease.

The problem with the clinical diagnostic process was that it subjected non-PD patients to a medication regime which had numerous potential side effects. Overall, the misdiagnosis rate in PD was variously reported, in research findings, at between 10%-24%, although neurologists often claimed that the rate had dropped to less than 5%. Kauffman (1998) observed a key problem in the differentiation between PD and Multiple System Atrophy (MSA):

...Data from PD brain banks showed how frequently the diagnosis of PD was incorrect; up to 10% of these brains turn out to have MSA. Indeed, Quinn (1994) recently pointed out that even Case 1 of James Parkinson's original description (1817), upon which much of his description of paralysis agitans was based, was probably suffering from MSA.”

The modern differentiation of MSA from PD is based upon MRI scans, with MSA patients exhibiting a cruciate appearance of the pons and hyperintense putaminal margins. In the absence of MRI based assessment, Kauffman (1998) noted that:

“Poor or no therapeutic response to Levodopa is a well known characteristic of MSA...”.

and so, the application of L-Dopa was a commonly used clinical testing approach. The various diagnostic paths related to PD are shown in Figure 1.

In addition to diagnostic issues, a fundamental problem with PD management is the idiosyncratic nature of the medication regime and the transitions from “on” to “off” which can become more pronounced as the disease progresses. A range of ancillary medications, such as COMT inhibitors, have reduced the severity of transitions but, fundamentally, there is still a case for determining the profile of PD patient mobility as a function of time of day and medication level. Such profiling can only take place if suitable tools are available. In the context of this research, if ABR characteristics demonstrated an intrinsic ability to provide a metric, then further research could seek to investigate the efficacy of biomedical tools.

1.2 The Auditory Brainstem Response and Impetus for Research

The ABR or brainstem evoked auditory response (BAER) is a commonly applied medical tool that is used to assess hearing, particularly in infants. Tests are performed by subjecting participants to audible clicking sounds and measuring the electrical response to those sounds. The derived ABR waveform is the ensemble average of the brain’s response to numerous “click” stimuli (typically hundreds). A typical waveform is shown in Figure 2, which is a modified abstraction from the American Speech and Hearing Association (ASHA).

The peaks of the transient ABR waveform are referred to as waves and the timing of each wave is referred to as its latency. The amplitude and timing of various waves reflect a range of neural phenomena, as summarized below:

"ABR Waves I and II correspond to true action potentials. Later waves may reflect postsynaptic activity in major brainstem auditory centres that comcomitantly contibute to waveform peaks and troughs. The positive peaks of the waveforms reflect combined afferent (and likely efferent) activity from axonal pathways in the auditory brain stem."

- www.emedicine.com/ent/topic473.htm (2004).

It was also postulated neurologists that Waves III and V of the ABR may, in fact, be a reflection of the postsynaptic activity in the structures where they are generated – these being the superior olive, and in the vicinity of the inferior colliculus. People with PD may have abnormalities in different neuronal groups of the central nervous system and those neuronal groups may undergo pathological changes as a result of the PD. Hence, there was a possibility that ABR may be influenced by the presence of PD.

At the time this research commenced, ABRs were in widespread use in clinical practice, particularly for the functional evaluation of brain-stem lesions –Hamilton and Starr (1976); Walser *et al.* (1982), Davis *et al.* (1985), Chiappa (1990), and Fischer and Bogner (1995). However, the possibility that postsynaptic changes, brought about by PD, could potentially be observed in the characteristics of Waves III – V of the ABR was one impetus for examining the technique in this research.

Another impetus for the examination of ABR in this research program was the linkage between the human brain's response to sound and the core body temperature. In fact, several investigators, including Stockard *et al.* (1978), Markland *et al.* (1987) and Sohmer *et al.* (1989), had found that the latencies of each component wave of the ABR progressively increased as a function of decreasing core body temperature, and that this effect was more profound on later components. Hypothermia in patients increased wave form peak latencies and decreased peak amplitude. Individual ABR components showed a slower rise time and became longer under hypothermic conditions.

As researchers and clinicians gained experience in measuring ABRs, different disorders that affected the latency of the ABR were also studied. One of these disorders was PD.

ABRs were measured by O'Donnell *et al.* (1987) in PD patients with therapeutic levels of Dopaminergic medication. Participants listened to a series of clicks, variable in both number and stimulus intensity, and had to count the occurrence of target tones of a higher frequency. The more prolonged the latency, the poorer a patient's performance on the test.

In summary, after an extensive review of research into ABR, there were essentially two speculative bases upon which it was hypothesized that there may be a relationship between ABR and PD. These were:

- (i) A number of researchers had found a strong correlation between ABR characteristics, particularly wave latency and thermoregulatory problems. A percentage of PD patients experienced marked thermoregulatory problems. Research published by Swinn *et al.* (2003) suggested that up to 64% of PD patients that they had tested suffered from sweating dysfunction associated with other symptoms of autonomic dysfunction..
- (ii) Earlier research had speculated that the genesis of the later ABR waves was based upon post-synaptic activity and, hence, that the diminution of this activity as a result of PD could therefore be manifest in the ABR. Specifically, that neuronal groups within the auditory pathway may be affected by PD and, hence, that PD may be manifest within the signature of the ABR.

Neither of these reasons were, of themselves, scientifically compelling but were considered of sufficient interest to undertake an exploratory research study whose outcomes could provide a basis for subsequent neuroscientific examination. It is the findings of the exploratory study that are reported herein. Moreover, it was determined that if such a study provided promising outcomes, then there were a number of areas of applied research that could be investigated to capitalize upon the potential diagnostic/monitoring outcomes in a biomedical instrumentation capacity.

The notion that a basic ABR test could replace traditional clinical neurological testing, founded upon years of practical experience, is somewhat simplistic and neurologists would generally argue that conventional tests such as the Unified Parkinson's Disease Rating Scale (UPDRS) provide reasonable indicators within approximately 15 minutes. The proposition here, however, is that if the ABR provides a reasonable measure of affliction, then the next stage of research would be to re-engineer the ABR test system to reduce the time taken for measurements to a few seconds, and potentially develop a wearable device that could provide profiling of medication performance over the course of a day.

2. Methods

2.1 Procedures

The experimentation program involved two groups of participants – a control group with no diagnosed history of neurological disorders, and a PD group, all of whom had been diagnosed (a minimum of one year earlier) by their neurologists as having the disorder. Each of these groups was subjected to a range of tests, with a focus on their ABR performance.

With no gold standard for diagnostics, axiomatically, there was no way of ensuring that 100% of PD participants actually had the disorder, or that 100% of the control group did not have the disorder, so an assumption had to be made that better than 90% of each participant group would either definitely have or definitely not have PD.

The control group was subjected to one experimental session. This involved:

- (i) Measurement of body temperature using a hospital-grade tympanic ear-probe thermometer
- (ii) Measurement of left and right ear ABRs.

The PD group was subjected to three experimental sessions that were designed to provide a systematic variation of medication level and diurnal factors for investigation. These sessions were defined as:

- (1) AM Session with PD participants medicated 90 minutes before testing (AM-On)
- (2) PM Session with PD participants at a medication low point (PM-Off)
- (3) PM Session with PD participants re-medicated (PM-On).

At each session, each PD participant was subjected to the following tests:

- (i) Measurement of body temperature using a hospital-grade tympanic ear-probe thermometer
- (ii) Assessment of Mobility based upon the Hoehn and Yahr (1967) staging process and based upon the modified Webster's Scale (1968) test.
- (iii) Measurement of left and right ear ABRs.

Each ABR test was performed twice for each ear.

The focus of the research was upon a group of people with mild manifestations of PD, in order to determine whether ABR parameters showed irregularities at a low level of movement dysfunction. Initially, a total of 15 PD participants and 15 control participants were recruited for the test program. After initial screening, it eventuated that one of the PD participants had a severe manifestation of the disorder and he was excluded. Another participant had been implanted with a Deep Brain Stimulator (DBS) device which interfered with ABR readings. Although the device could have been disabled, this would have required the participant to wait for an additional hour for the effect to wear off and this was deemed impractical. Hence, of the original 15 PD participants, 13 went through to the full test program.

The PD participants were chosen to have a spread of ages, and ranged from people with young-onset manifestations of PD to elderly people with mature-onset manifestations. All the PD participants used a basic L-Dopa medication regime, together with ancillary pharmaceuticals, to smooth transitions from "on" to "off". In terms of the number of years since their initial diagnosis, participants ranged from 1 to 13 years since the disorder was diagnosed by their neurologist. The control group of 13 people was approximately age and gender matched to the PD group.

PD participants were tested in what were referred to as “on” and “off” modes for their medication. In reality, it would have taken a minimum of 12 hours for a washout in medication levels of PD participants, so technically, they were never fully “off”. For the purposes of this research, however, the afternoon sessions were timed to be at a point of re-medication, so participants had decreased mobility and, for practical purposes, were considered to be “off”.

The key results derived from the experiments were subjected to three forms of statistical analysis:

- (i) Analysis of Variance (ANOVA)
- (ii) Permutation Analysis
- (iii) Student’s t-test.

These tests provided some indication of the significance of the various results (specifically the “p” values). The p-values in the permutation test were generated using a paired, one-sided permutation test in which all permutations were calculated. The code for the analysis was developed based upon the approach in the text by Good (2000).

In particular, the value of the permutation test was that it did not assume a Gaussian distribution of results and provided a better indication of p-value than the traditional Student’s t-test which was applied for the sake of completeness.

2.2 Limitations of Procedures

The ABR machine that was employed to undertake the study required a manual measurement of ABR peaks. The manual identification and measurement of Wave III and V peaks presented a potential source of error and subjectivity. Given sufficient

resources, this subjectivity would normally be removed by having such measurements undertaken by an individual who was blind to the study. However, in this case, this was not practical. In order to reduce the degree of subjectivity associated with the presented results, it was decided to introduce measurements based upon what the researchers referred to as the “Best” waveform. For any one participant, this referred to the measurements derived from the ABR waveform (for either the left or right ear) that provided (what the researchers agreed to be) the most clearly identifiable Wave III and V peaks – that is to say, minimum ambiguity, rather than the most convincing numerical outcome. Hence, the results presented as “Best” are the ones to which the researchers ascribed the highest degree of confidence (or the lowest level of subjectivity).

Another limitation of the study was clearly the small size of the participant groups. However, when subjected to basic statistical analysis, the results presented herein show some clear trends which would benefit from a much larger study, with segmented groups of PD participants, divided according to disease severity, level of dysfunction, etc.

It was earlier noted that in PD, a medication washout is generally assumed to be more than 12 hours. The commonly used practice for medication “off” is overnight withdrawal of medication. This was not practical for this particular study, and so what is presented as medication “off” is technically a low level of medication, with increased level of dysfunction as measured by Webster’s mobility index.

The ABR test has a number of limitations, not the least of which is the fact that its performance is influenced by various hearing impairments, so a literature review was undertaken to determine the various factors that influenced the morphology of ABR waveforms, including stimulus factors, the presence of other conditions, such as Multiple Sclerosis, etc. These factors were reported in detail in Yousefi (2004).

3. Results

3.1 Clinical Observations

Of the 13 PD participants, 10 had subjective symptoms relating to autonomic nervous system (ANS) dysfunction. The common ones were:

- Postural dizziness (10 participants)
- Urinary function problems (8 participants)
- Bowel function problems(5 participants).

None of the 13 participants in this group had any complaints about disturbances related to sweating. In other words, there were no marked signs of thermoregulatory problems in these mildly afflicted participants. Of the 13 participants, 12 reported that they had sleep disturbance problems that were of concern to them.

All 13 participants were tested and scored according to modified Hoehn and Yahr and modified Webster rating scores for mobility.

In order to qualify for the full test program, participants with Parkinson's Disease had to be at Stage One (Signs and symptoms on one side only) of the Hoehn & Yahr classification. They also had to have a Webster's score of less than 10 when their medication was "on" medication and not more than 16 when their medication was "off".

Summarised below are the highlights of the clinical findings derived from the modified Webster Rating Score, ranging from the most pronounced dysfunction to the least pronounced:

(i) Rigidity

All the participants suffered from severe rigidity, regardless of whether their medication was on or off – the level of rigidity did not vary significantly.

(ii) *Balance*

Control of balance was the second most important issue that these mild PD patients were facing. Their balance was slightly better when their medication was “on” than when it was “off”. Males scored better than females.

(iii) *Bradykinesia of hand*

With medication “on”, 12 of the PD participants had hand movements that were almost normal and their scores were good. On one of the PD participants, the Bradykinesia did not vary significantly whether the medication was “on” or “off”.

(iv) *Tremor*

While the PD participants had their medication “on” they had no visible signs of tremor but as soon as the medication affect started to diminish, the tremors started to emerge.

(v) *Gait*

Mild PD participants in this study did not show any significant problems concerning gait. Regardless of them being in a medication “on” or “off” state, their scores for gait were essentially normal.

(vi) *Upper extremity swing*

12 of the participants had no difficulties with extremity swing, regardless of whether medication was “on” or “off”. One of the participants could not swing their arm but did not remember if the problem started after or before their illness.

(vii) *Posture*

The difficulty of observing postural irregularities was the time it took to be apparent to the participant and to the people around the participant. In our observations, the mildly affected participants had to be at the peak of

their need for medication (not taking their medication for whole day) to have any affect on their posture.

(viii) Arising from a chair

None of the Parkinson's participants had any difficulty arising from a chair regardless of whether their medication was "on" or "off".

(ix) Facies (facial expression)

There was no sign of abnormal animation on our mildly affected participants either before or after medication.

(x) Speech

All the PD patients had good clear, loud, resonant, easily understood speech.

(xi) Seborrhoea

There was no detection of obvious oiliness present in any of the participants.

(xii) Self-care

All the Parkinson's participants in this study were able to provide full self-care and were able to live independently.

3.2 Experimental Results

The parameter list for the experimental results derived from the testing is shown in Table 1. Of particular note in terms of the parameter labels is the use of the term “Best” or “B” which, as previously noted, provided the least subjective measurement outcome for any given participant (either left or right ear) and the one to which the researchers ascribed the highest level of confidence. Average (A) refers to the average of left and right ear results.

An overview of the experimental results is shown in Table 2, which shows the results simply averaged across groups for various experiments. The complete statistics are presented in Table 8. The following observations were made from the raw waveforms and simple averages of numerical values:

- (i) In their medication “off” state, all 13 PD participants presented with ABR waveform morphologies that differed markedly from their “on” state and, indeed, from the typical morphology of the control group.
- (ii) The individual participant results for Wave III and V amplitudes are shown in Figure 3. Figure 3 also shows that despite differences in level of dysfunction between PD group participants, there was no overlap between results for control group participants and unmedicated PD participants. Neither was there any overlap between medicated and unmedicated participants. In Figure 3 it can also be observed that two of the PD participants (Numbers 3 and 10) gave outlying results, so the various statistical analyses were performed including and excluding their impact so that a complete picture could be obtained.
- (iii) PD Mobility (Parameter M), as measured via the Webster’s Modified Scale, varied with medication levels as expected. The mobility index was used as an indicator to determine whether medication was on or approaching “off”. The 13 PD participants demonstrated a mild level of disability, based upon

the Webster's Scale, even when medication was nearing "off". The results for mobility are shown in Table 3.

- (iv) None of the PD group or control group participants presented with temperature irregularities. In clinical evaluations conducted during the experimentation program, none of the PD group participants reported any signs of sweating dysfunction. The basic temperature measurements (Parameter T) are shown in Table 4 for both control and PD participants. A body temperature irregularity in either the control or PD participants would have been reflected in latency variations in the ABR waveforms. As there were no temperature irregularities, any irregularities in the ABR latencies would have to have been a function of other factors.
- (v) The latency of ABR Wave III (Parameter E) and the latency of Wave V (Parameter F) appeared to be insensitive to the presence of PD or to variations in medication levels.
- (vi) The Amplitude of ABR Wave III (Parameter X) appeared to be sensitive to both the presence of PD and to variations in medication levels.
- (vii) The Amplitude of ABR Wave V (Parameter Y) appeared to be sensitive to the variation of PD medication levels but not to the presence/absence of PD.

In order to determine the significance of the results, particularly as they pertained to Parameters X and Y, the results were initially subjected to an analysis of variance. The results of the ANOVA are shown in Table 5, including and excluding Participants 3 and 10. The ANOVA suggests an extremely low probability of a null hypothesis in the case of Parameter X, and a less convincing result for Parameter Y. In other words, there was a very high probability of a significant variation in ABR Wave III amplitude across the control and PD groups. Following the ANOVA, the ABR parameters were then subjected to a computer-based permutation test and to a conventional Student's t-test to

determine the significance that could be ascribed to them. The results are shown in Tables 6 and 7. The results confirm that there is a high probability that:

- (I) ABR Wave III Amplitude may be able to differentiate between PD afflicted people and a control group, even when the PD people are fully medicated
- (II) ABR Wave III Amplitude may be able to differentiate between medicated PD and unmedicated PD people.
- (III) ABR Wave V Amplitude may be able to differentiate between medicated PD and unmedicated PD people.

The statistics also suggest that there is little information pertaining to PD that is contained in either Wave III or V latencies.

4. Discussion

The results derived from this experimental research suggest that there is significant statistical merit in pursuing ABR Wave III and V amplitudes and their relationship with PD and medication levels. Of particular importance would be the need to:

- (i) Independently reproduce the results presented herein with a different PD group and control group. Ideally, calculation of Wave III and V amplitudes would need to be performed by a person blind to the study group in order to provide an impartial assessment of what has been presented herein.
- (ii) Extend the study, presented herein, to include severely afflicted PD participants, and to determine whether or not ABR Wave III and V amplitude levels decline even further as mobility decreases (i.e., mobility index increases). Specifically, a much larger study needs to be undertaken including PD participants with varying degrees of dysfunction and immobility to determine the sensitivity of the test to variations in the disorder itself.
- (iii) Extend the study, presented herein, to include participants with MSA and PD, or indeed other Parkinsonian afflictions, to determine whether there is any differential information contained with the ABR.

For more than three decades, the macro effect of PD medication has been assessed through conventional clinical tests, such as the Unified Parkinson's Disease Rating Scale (UPDRS) and Webster's Mobility test. The problem with such tests is that they have a degree of subjectivity and they take a significant amount of time to perform – potentially 15 - 30 minutes per participant. This limits their usefulness in terms of monitoring medication effectiveness. However, if it eventuates that ABR Wave III and V amplitudes do provide a high degree of correlation with mobility, then a cost-effective tool could potentially be developed for on-line monitoring of medication effectiveness. This would have significant applications in measuring the macro performance of pharmaceutical agents by profiling over a 24 hour period. The potential

for utilizing ABR characteristics for PD diagnostic applications and disease progression also presents a range of new possibilities for the field.

The obvious corollary of this research is to understand the physiological genesis of the phenomena that have been presented. A self-evident shortcoming of this research is that it only provides a speculative physiological basis by which such phenomena may have arisen – largely the possibility that neuronal groups in the auditory pathway may be influenced by PD and that these irregularities are then manifest in the ABR. However, given the strength of the correlations observed in this exploratory study, it is recommended that further research be undertaken to explore the genesis of the phenomena.

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7. Tables and Figures

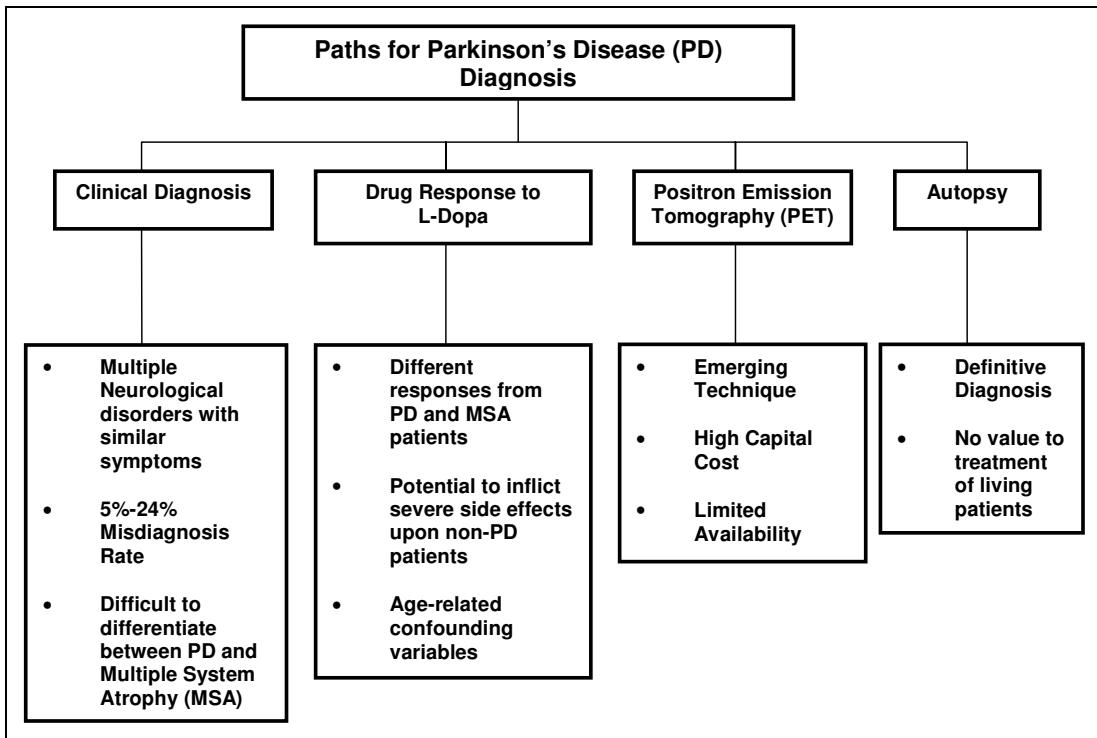


Figure 1 – Diagnostic Paths for PD

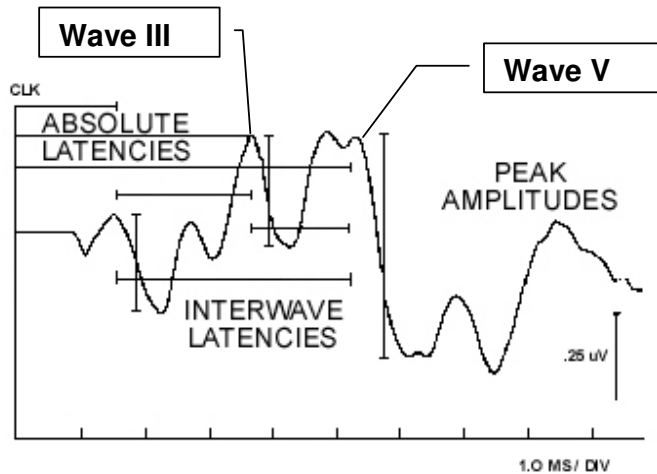


Figure 2 – Typical ABR Ensemble Waveform (abstracted from the ASHA)

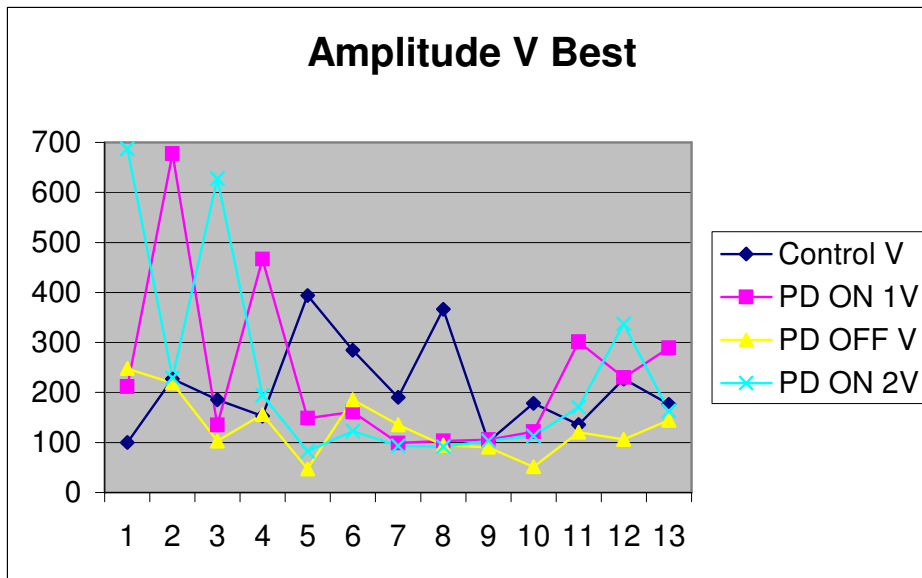
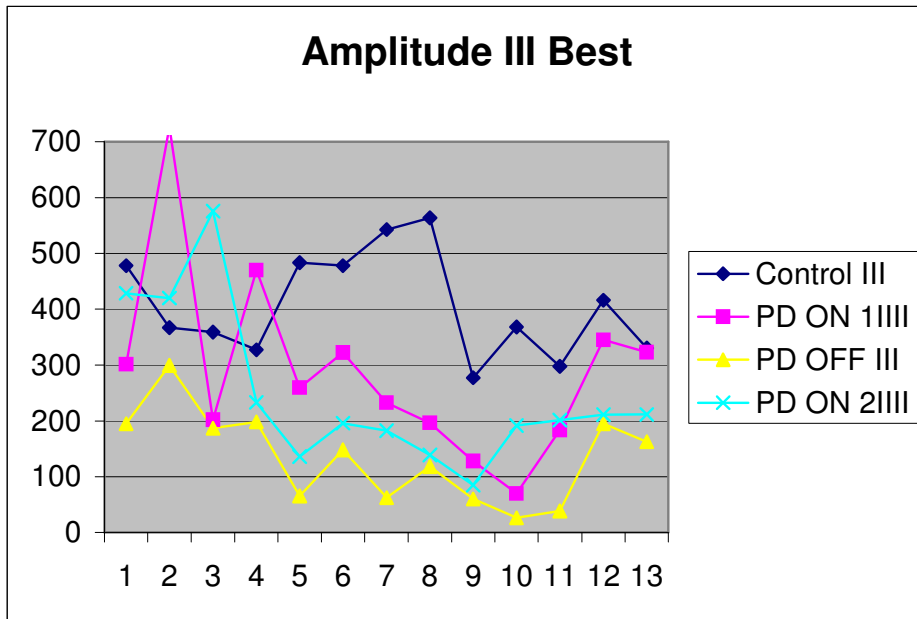


Figure 3 – Individual Participant Results for Amplitudes of Waves III and V
Y-Axis is in nano-Volts, X-Axis Represents Participant Number

Table 1 – Key to Parameters Used in Experimental Results

<i>Abbreviation</i>	<i>Parameter</i>
1	AM Session for PD Patients with Medication Fully “On”
2	PM Session for PD Patients with Medication Approaching “Off”
3	PM Session for PD Patients with Medication Fully “On”
A	Average of Left and Right Ear Results
B	Best case of Left or Right Ear Results
E	ABR Wave III Latency
F	ABR Wave V Latency
L	Left Ear Results
M	Mobility Derived from Modified Webster’s Test
R	Right Ear Results
T	Temperature
X	ABR Wave III Amplitude
Y	ABR Wave V Amplitude

Example 1: FIL = ABR Wave V Latency for Left Ear (PD Group)
 Example 2: XR = ABR Wave III Amplitude for Right Ear (Control Group)

Table 2 – Overview of Experimental Results – Averaged Over Group

<i>Parameter</i>		<i>Control</i>	<i>PD 1 (ON)</i>	<i>PD 2 (OFF)</i>	<i>PD 3 (ON)</i>	<i>General Observation</i>
<i>M</i>	A	0	7.9	13.2	7.0	PD Mobility variation with medication level
<i>T (°C)</i>	L	36.3	36.1	36.2	36.3	No Irregularities noted in control or PD group
	R	36.2	36.5	36.4	36.4	
<i>X (nV)</i>	L	403.9	239.0	136.9	230.5	ABR Wave III amplitude varies with PD and medication levels.
	R	317.4	228.3	127.8	218.1	
	B	406.9	289.4	135.2	247.1	
	A	357.8	237.8	130.2	217.6	
<i>Y (nV)</i>	L	181.1	199.5	131.3	233.4	ABR Wave V amplitude varies with medication levels
	R	177.3	207.1	91.9	188.5	
	B	209.1	234.5	130.7	231.9	
	A	178.5	200.3	112.3	194.8	
<i>E (mS)</i>	L	5.8	5.6	5.5	5.6	No discernible trend
	R	5.9	5.7	5.8	5.7	
	B	5.8	5.7	5.7	5.7	
	A	5.8	5.7	5.6	5.6	
<i>F (mS)</i>	L	7.4	6.3	7.5	7.4	No discernible trend
	R	7.3	7.3	7.6	7.4	
	B	7.4	7.4	7.5	7.4	
	A	7.4	6.9	7.5	7.4	

Table 3 – PD Participant Mobility as a function of Sessions

PD Participant Number	Years Since Diagnosis	M1 AM-On	M2 PM-Off	M3 PM-On
1	11.5	8	15	8
2	3	9	12	6
3	3	6	11	7
4	5	9	13	6
5	6	13	17	9
6	13	6	14	4
7	5	6	13	7
8	6	6	12	5
9	10	9	14	9
10	13	9	13	9
11	10	8	14	8
12	1	6	11	6
13	3	8	12	7
Average		7.9	13.2	7

Table 4 – Participant Temperature as Measured by Tympanic Thermometer

Control		PD Group AM-ON		PD Group PM-OFF		PD Group PM-ON	
Average Mobility M = 0.0		Average Mobility M1 = 7.9		Average Mobility M2 = 13.2		Average Mobility M3 = 7.0	
TL	TR	T1L	T1R	T2L	T2R	T3L	T3R
36.3	35.8	36.3	37.1	36.5	36.9	36.5	36.8
36.2	36.1	36.2	36.4	36.1	36.3	36.1	36.3
36.7	36.8	36.1	36.0	36.4	36.6	36.6	36.1
36.1	35.9	36.3	36.5	36.1	36.8	36.1	36.8
35.8	36.0	36.0	36.0	36.5	36.2	36.8	36.2
36.8	36.7	36.2	36.1	35.4	36.1	36.4	36.7
36.8	36.7	35.4	36.2	35.9	36.0	36.2	36.1
36.5	36.0	36.3	36.3	36.3	36.2	36.5	36.5
36.2	35.7	36.0	36.1	36.7	36.0	36.3	35.7
35.7	35.5	36.4	35.5	36.4	36.7	36.3	36.1
36.0	36.3	36.6	36.8	36.5	37.1	37.0	37.1
37.7	37.0	36.2	36.3	36.3	36.6	36.3	36.6
36.2	36.5	35.4	35.4	36.3	36.4	36.3	36.3

Table 5 – ANOVA Results for ABR Wave III and V Amplitudes

ANOVA Test Comparison	Conditions	P Result
XB, X1B, X2B, X3B	Participants 3 & 10 Included	0.000021545
XB, X1B, X2B, X3B	Participants 3 & 10 Excluded	0.0000182382
X1B, X2B, X3B	Participants 3 & 10 Included	0.017029635
X1B, X2B, X3B	Participants 3 & 10 Excluded	0.00789701
YB, Y1B, Y2B, Y3B	Participants 3 & 10 Included	0.224594972
YB, Y1B, Y2B, Y3B	Participants 3 & 10 Excluded	0.296119088
Y1B, Y2B, Y3B	Participants 3 & 10 Included	0.168919805
Y1B, Y2B, Y3B	Participants 3 & 10 Excluded	0.216460065

Table 6 – Permutation Analysis of Results

Test	P. of Null Hypothesis (Amplitude)	P. of Null Hypothesis (Latency)
PD-On-AM Wave III against Control Group Wave III	X1 against X 0.02710*	E1 against E 0.41785
PD-Off-PM Wave III against PD-On-AM Wave III	X2 against X1 0.00012*	E2 against E1 0.46582
PD-On-PM Wave III against PD-On-AM Wave III	X3 against X1 0.19971	E3 against E1 0.38513
PD-On-AM Wave V against Control Group Wave V	Y1 against Y 0.33228	F1 against F 0.46216
PD-Off-PM Wave V against PD-On-AM Wave V	Y2 against Y1 0.00623*	F2 against F1 0.35828
PD-On-PM Wave V against PD-On-AM Wave V	Y3 against Y1 0.48413	F3 against F1 0.47559

*Pr < 0.05 Indicates a significant Result

Table 7 – Student’s t-test Results

<i>Test</i>	<i>P. of Null Hypothesis (Amplitude)</i>	<i>P. of Null Hypothesis (Latency)</i>
PD-On-AM Wave III against Control Group Wave III	X1 against X 0.03937*	E1 against E 0.80816
PD-Off-PM Wave III against PD-On-AM Wave III	X2 against X1 0.00023*	E2 against E1 0.92860
PD-On-PM Wave III against PD-On-AM Wave III	X3 against X1 0.39977	E3 against E1 0.77315
PD-On-AM Wave V against Control Group Wave V	Y1 against Y 0.64002	F1 against F 0.91800
PD-Off-PM Wave V against PD-On-AM Wave V	Y2 against Y1 0.02481*	F2 against F1 0.72281
PD-On-PM Wave V against PD-On-AM Wave V	Y3 against Y1 0.61211	F3 against F1 0.94651

*Pr < 0.05 Indicates a significant Result

Table 8 – Basic Statistics for All ABR Parameters

<i>Item</i>	<i>Group</i>	<i>Abbreviation</i>	<i>Grp. Avege</i>	<i>Grp. Std. Dev.</i>	
Measured Temperature (T)	PD	T1L	36.11	0.35	
	PD	T2L	36.21	0.46	
	PD	T3L	36.26	0.33	
	PD	T1R	36.45	0.36	
	PD	T2R	36.42	0.26	
	PD	T3R	36.41	0.38	
	CTRL	TL	36.30	0.37	
	CTRL	TR	36.20	0.41	
	ABR Wave III Amplitude	PD	X1L	238.96	111.66
PD		X2L	136.89	59.71	
PD		X3L	230.52	89.10	
PD		X1R	228.34	111.13	
PD		X2R	127.83	72.22	
PD		X3R	218.09	111.99	
PD		X1B	289.39	167.09	
PD		X2B	135.21	81.05	
PD		X3B	247.06	140.13	
PD		X1A	237.83	86.69	
PD		X2A	130.23	62.30	
PD		X3A	217.55	84.37	
CTRL		XL	403.87	76.75	
CTRL		XR	317.40	78.40	
CTRL		XB	406.85	93.86	
CTRL		XA	357.81	53.26	
ABR Wave V Amplitude		PD	Y1L	199.45	89.49
		PD	Y2L	131.27	65.55
	PD	Y3L	233.39	175.34	
	PD	Y1R	207.01	177.98	
	PD	Y2R	91.88	31.17	
	PD	Y3R	188.53	126.65	
	PD	Y1B	234.52	169.85	
	PD	Y2B	130.67	59.91	
	PD	Y3B	231.94	201.88	
	PD	Y1A	200.31	123.84	
	PD	Y2A	112.32	36.344	
	PD	Y3A	194.79	142.20	
	CTRL	YL	181.10	83.99	
	CTRL	YR	177.34	77.31	
	CTRL	YB	209.09	91.40	
	CTRL	YA	178.45	76.21	

Table 8 Continued Next Page...

<i>Item</i>	<i>Group</i>	<i>Abbreviation</i>	<i>Grp. Avge</i>	<i>Grp. Std. Dev.</i>
ABR Wave III Latency	PD	E1L	5.55	0.717
	PD	E2L	5.50	0.29
	PD	E3L	5.60	0.28
	PD	E1R	5.74	0.70
	PD	E2R	5.78	0.39
	PD	E3R	5.65	0.38
	PD	E1B	5.73	0.66
	PD	E2B	5.72	0.40
	PD	E3B	5.67	0.36
	PD	E1A	5.66	0.58
	PD	E2A	5.64	0.22
	PD	E3A	5.64	0.28
	CTRL	EL	5.79	0.40
	CTRL	ER	5.86	0.41
	CTRL	EB	5.78	0.38
	CTRL	EA	5.83	0.35
ABR Wave V Latency	PD	F1L	6.30	0.68
	PD	F2L	7.48	0.57
	PD	F3L	7.39	0.43
	PD	F1R	7.33	0.61
	PD	F2R	7.61	0.52
	PD	F3R	7.38	0.33
	PD	F1B	7.40	0.58
	PD	F2B	7.46	0.52
	PD	F3B	7.41	0.36
	PD	F1A	6.88	0.60
	PD	F2A	7.48	0.26
	PD	F3A	7.42	0.22
	CTRL	FL	7.44	0.32
	CTRL	FR	7.26	0.36
	CTRL	FB	7.38	0.37
	CTRL	FA	7.36	0.28
Webster's Scale Mobility	PD	M1	7.92	2.02
	PD	M2	13.15	1.68
	PD	M3	7.00	1.58