Investigating the viability of motoric task performance as a clinical biomarker in Huntington's and Parkinson's disease

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Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other University or Institute of learning.

Abstract

Evaluating hand tapping as a clinical biomarker in Parkinson and Huntington's diseases, using an Android device was the objective of the study. A novel hand - tapping tool using an Android OS was developed over a year, which included 5 tapping tasks. The application was meant for installation on Samsung Galaxy 7" tablet devices. The tasks included finger tapping; metronome based tapping, simple and choice reaction time and was used to study a cross section of 45 controls of three different age groups, from 20-30 years, 35 -45 years and 65-80 years. Age and gender matched controls to Parkinson's subjects (n=21) and Huntington's disease patients (n=17) were assessed using the same tapping tasks. Baseline values for various tapping measures such as tapping rate, inter-tap interval, force, pro-tap (simple) reaction time, anti-tap(choice) reaction time were obtained. The study reported a significant difference between 20-30 year olds and 65-80 year olds in tapping rates and inter-tap-interval of the double target tapping task. Displacement, pro-tap time and anti-tap times were lower in 20-30s and 35-45 year olds compared to the 65-80s group. PD patients showed markedly lower values and were significantly different from controls in tapping rates, displacement of single target tapping, tapping rates and inter-tap-interval of double target tapping, pro-tap and anti-tap times and their standard deviation. HD patients had significantly lower values in inter-tap-intervals, displacement of single finger tapping, tapping rates, inter-tap interval and displacement of double target tapping, pro-tap and anti-tap reaction times. In conclusion, the study enabled us to identify tapping parameters and reaction time tests which

have the potential to differentiate between Parkinson's and Huntington's patients with controls, therefore making motoric task performance a potentially viable clinical biomarker in HD and PD.

Glossary

PD: Parkinson's disease

HD: Huntington's disease

BG: Basal ganglia

SMA: Supplementary motor area

PMC: Pre-motor cortex

STN: Subthalamic nucleus

SNPc : Substantia nigra pars compacta

SNPr: Substantia nigra pars reticulata

GPi: Globus pallidus internal segment

IPD: Idiopathic Parkinson's disease

PMG: Pre-manifest gene carriers

MG: Manifest gene carriers

UHDRS: Unified Huntington's disease rating scale

UPDRS: Unified Parkinson's disease rating scale

DCL: Diagnostic level

TMS: Total motor score

EDI: Edinburgh inventory

ITI: Inter-tap-interval

RT: Reaction time

ER: Error rate

EC: Error count

SRT: Simple reaction time/Serial reaction time

CRT: Choice reaction time

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Chapter 1

Introduction

1.1 Movement Disorders

Movement disorders are a category of neurological disorders characterized by either an excess or decrease of normal movements. These neuro-motor abnormalities may affect any aspect of movement, which may include its production, control and/or quality.

Normal movement involves a complex system of control. Movement is produced and coordinated by several interacting structures of the brain, including the neocortex, basal ganglia, motor cortex, cerebellum, brainstem along with the spinal cord and its interacting pathways. As movement, both voluntary and involuntary, involves a highly organized yet complex circuit, an abnormality in any of the above structures, their input or output, can affect movement.

These disorders are characterized by abnormal movements (dyskinesias), by poverty of movement (bradykinesia/akinesia), or by disturbance in the execution of movements (ataxia) and encompass pyramidal disorders, cerebellar disorders, basal ganglial disorders (Parkinsonian syndromes, Huntington's

disease, dystonias) and other motor disturbances. Movement disorders can be caused by degenerative conditions of environmental or genetic origin or by non-degenerative conditions such as trauma. Simplistically, movement disorders are more often classified as hypokinetic or hyperkinetic. Hypokinetic would refer to a decrease in voluntary or inability to perform voluntary action, while hyperkinetic refers to increase in voluntary movement or lack of control over movement. The pathophysiologic mechanisms of both types can at least in part be attributed to a dysfunction in the basal ganglia circuits.

Movement disorders can be categorized as follows:

1. Pyramidal
2. Basal ganglia
3. Cerebellar

The above classification is based on the anatomy of the motor system, the location of the lesion and the type of abnormal movement they produce or fail to produce.

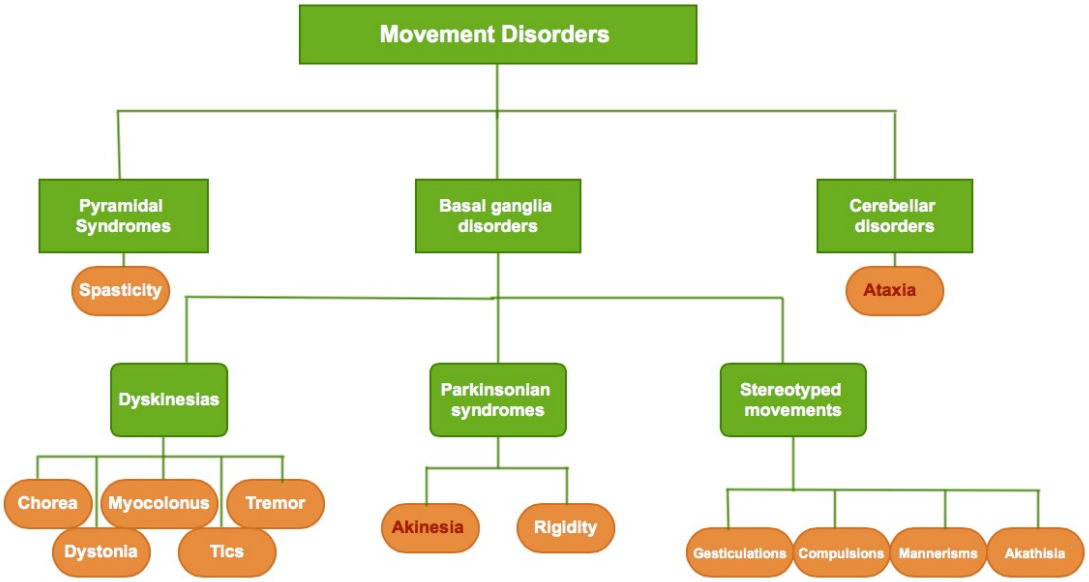


Fig 1.1: Anatomical classification of movement disorders. Text marked in red denote negative motor signs, white denotes positive motor signs.
(Source: Alabanese et al, 2003, Kandel (2012): Principles of Neural Science)

1.2 The Basal Ganglia

Basal ganglia are a collection of five interconnected subcortical nuclei. These are the striatum, which comprises of the putamen and caudate nucleus, along with the globus pallidus , subthalamic nucleus, and substantia nigra.

1. Putamen
2. Caudate nucleus
3. Globus Pallidus interna (GPi) and external segment (GPe)
4. Subthalamic nucleus (STN)
5. Substantia nigra pars compacta (SNPc), Substantia nigra pars reticulata (SNPr)

The major input to the basal ganglia is from the cortex, pre-motor cortex, supplementary motor area (SMA), the substantia nigra pars compacta(SNPc)and the centromedian nucleus of the thalamus, with some minor input from the amygdala and the hippocampus. The final output of the basal ganglia is to the cortex, pre-motor cortex and SMA. The striatum receives input from the cortex, thalamus, brainstem and SNPc and projects to the output nuclei via direct and indirect pathways. The basal ganglia via the internal pallidal segment (GPi) and substantia nigra pars reticulata (SNPr) send output messages to the motor cortex, helping to initiate movements, and control muscle tone. Most of the neurons are GABAergic and inhibitory within the caudate nuclei, putamen and the globus pallidus (GPi), while in the subthalamic nuclei, they are glutaminergic and excitatory.

1.3 Motor loop

I shall restrict our discussion to voluntary, purposeful movements, which primarily involve the motor and sensory cortex, basal ganglia, cerebellum, brainstem and spinal cord.

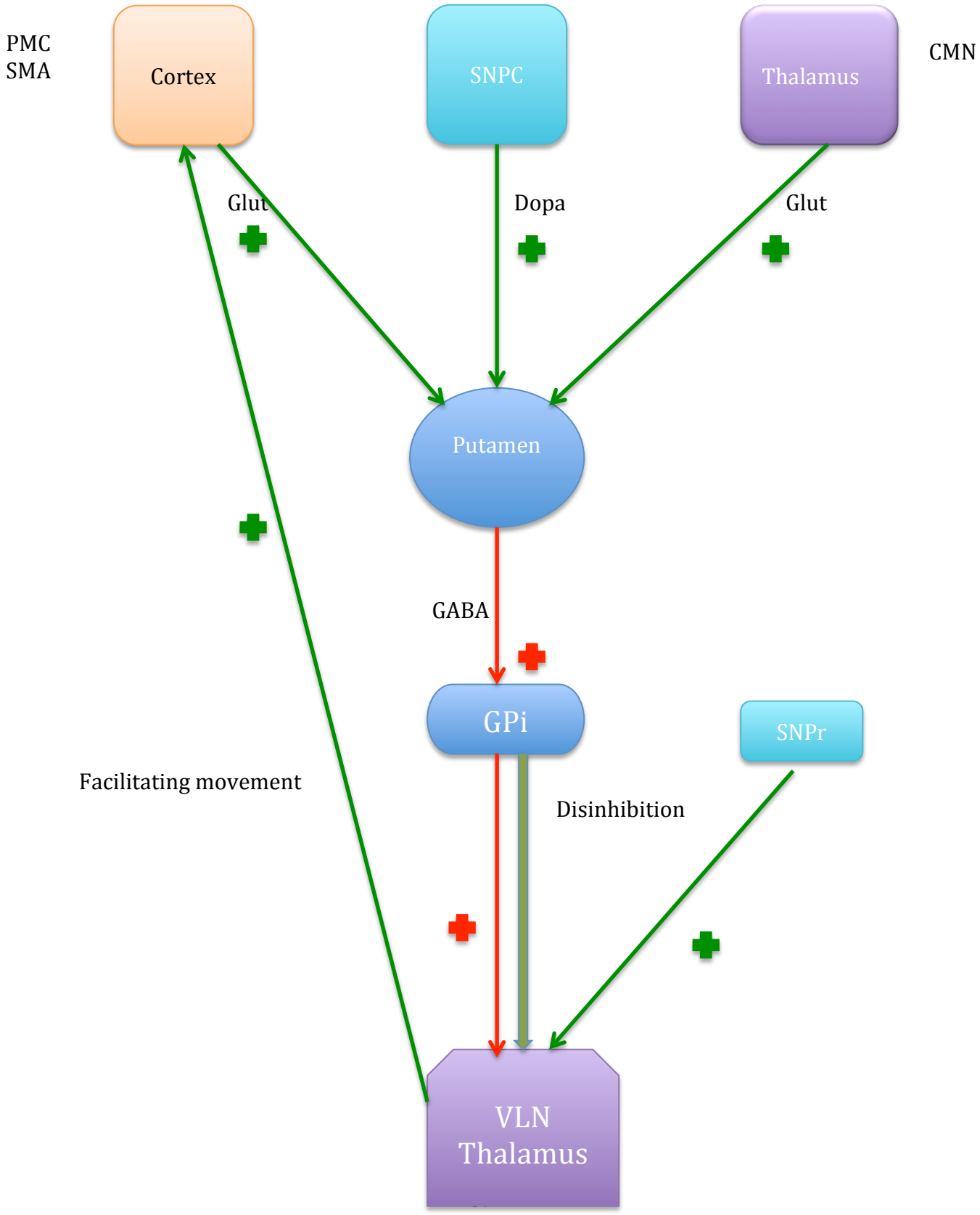
For ordinary movement to take place, the brain receives input through the eyes, ears, and tactile proprioception, and sends signals via the cortex, SNPC, centromedian nucleus of the thalamus to the striatum. The input from the cortex (Area 4, and Area 6), are glutaminetgic or excitatory to the striatum, the input from the SNPC is dopaminergic. The Striatum through the GABAergic system is inhibitory to the Globus pallidus, which in turn is inhibitory to the Ventro lateral thalamus.

So when the excitatory signals arrive at the striatum, it inhibits the GP. Since the GP has been inhibited, it can no longer inhibit the VL thalamus, which sends excitatory signals to the cortex through glutaminergic connections. This is the **motor loop**, which takes place during normal movement.

The two components in this include the direct and indirect motor loop. The direct pathway includes D1 neurons and the indirect pathway includes D2 neurons.

Fig 1.2 Direct pathway of the motor loop (facilitating movement)
The direct pathway causes facilitation of movement by glutaminergic excitation of the putamen which inhibits the Globus pallidus interna , thereby disinhibiting the ventro lateral nucleus of the thalamus leading to cortical excitation causing movement. Inhibition is shown in red and is GABA mediated. Excitation is either glutaminergic or dopaminergic and is shown in green

Motor Loop - Direct pathway



Motor Loop – Indirect Pathway

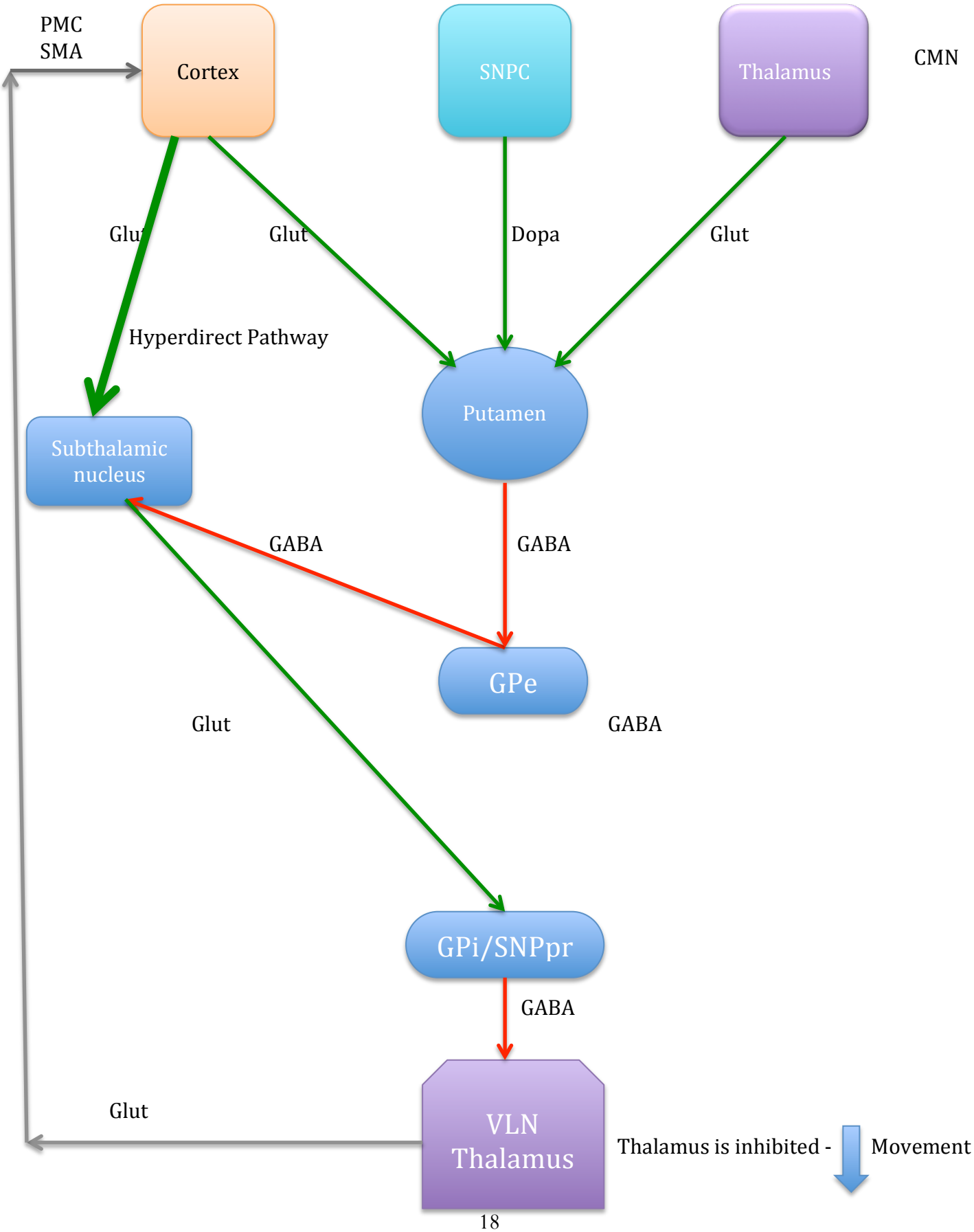


Fig 1.3 Indirect pathway of the motor loop (restricting movement)
The indirect pathway reduces movement by glutaminergic excitation of the putamen leading to a inhibition of the globus pallidus externa causing a disinhibition of the subthalamic nucleus (STN). STN's glutaminergic excitation of the GPi is achieved, which inhibits the VLN of the thalamus, reducing its cortical output and therefore, movement.

The direct pathway as illustrated above begins with the input from the cortex to the striatum, which through its GABAergic transmission inhibits the GPi, which disinhibits the Thalamus. The indirect pathway passes from the striatum to the subthalamic nucleus through its inhibitory/GABAergic pathway, which supports the STN in providing an excitatory stimulus to the GPi, which in turn disinhibits the thalamus, and brings about a decreased excitation of the cortex, completing the motor loop. Though we aim to understand them as different pathways, the two pathways are not completely separate. It must be understood that the input to the STN is not merely from the Striatum in the indirect pathway, but also from the frontal lobe through the hyper direct pathway. Therefore, when cortical mechanisms initiate a voluntary movement, through the direct pathway, the GPi is inhibited, which leads to the disinhibition of the VL Thalamus. Parallel to which, the indirect pathway via the Striatum to the STN, and the hyper direct pathway via the frontal lobe to STN, both excite the GPi through their glutaminergic connection. The net result of these would be the voluntary movement as the inhibitory action on the GPi is stronger albeit slower (Kandel (2012): *Principles of Neural Science*, Bear & Connors (2007): *Exploring the brain*).

Motor loop – All pathways

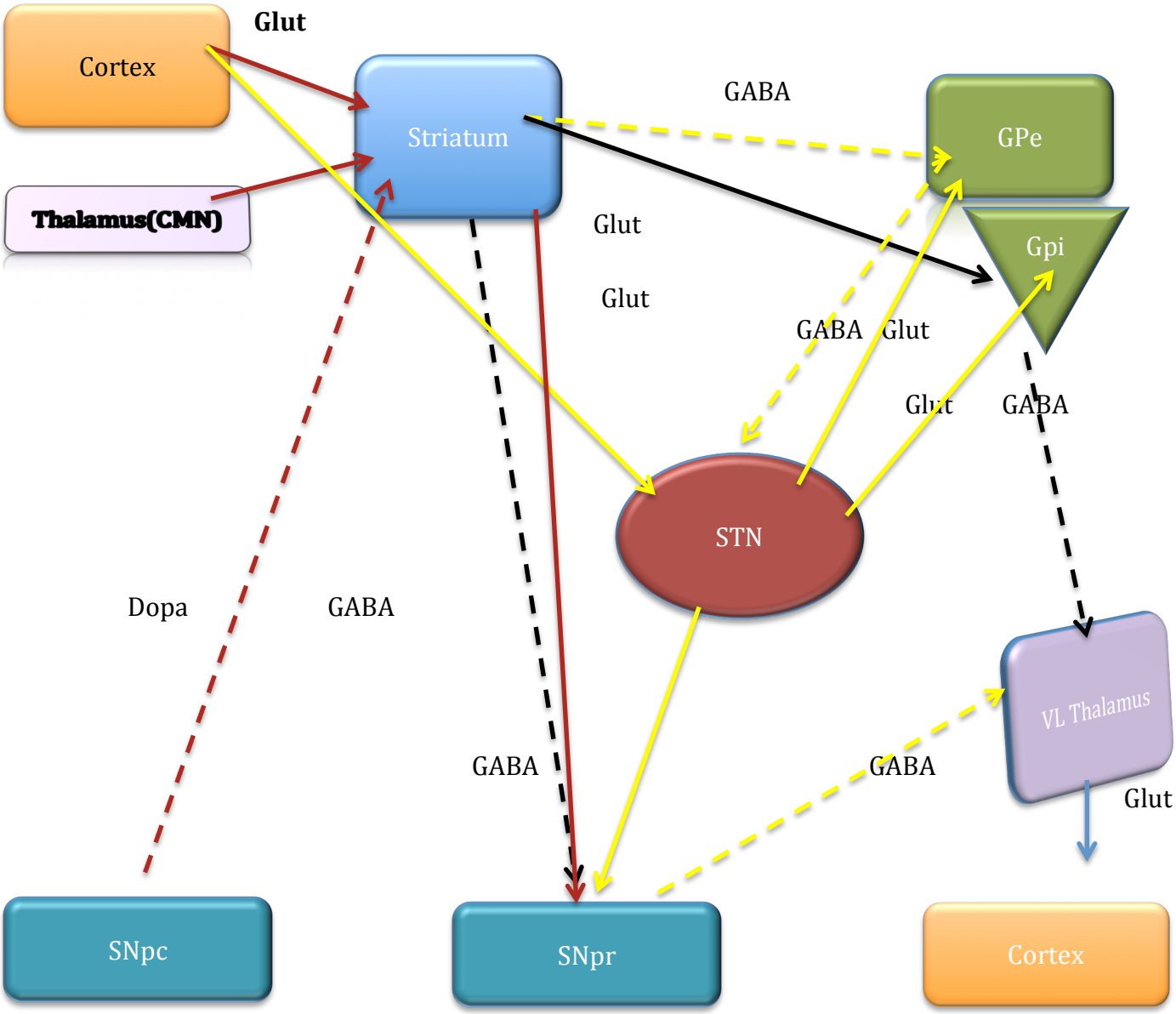


Fig 1.4 Motor loop (both pathways)

Both indirect, direct and hyperdirect pathways interact with each other to cause normal movement. Overexpression of any/or all the pathways will cause either a net increase or decrease in movement, which may or not be coordinated.

This model is also used to explain other basal ganglia disorders. In hypokinetic states, the activity in the indirect pathway predominates over that of the direct pathway, giving rise to an increase in GPi inhibitory output, which results in decreased motor activity and hypokinesia. In hyperkinetic states, the activity in the indirect pathway is decreased, giving rise to a decreased inhibitory output from the direct pathway, which results in excess motor activity.

Typical examples of these hypokinetic and hyperkinetic movement disorders are Parkinson's and Huntington's disease.

My study relates to these two specific neurodegenerative conditions, which cause movement disorders and I will restrict discussion to the same.

Chapter 2

Parkinson's Disease

2.1 Introduction

Almost 200 years ago, James Parkinson described 'The Shaking palsy', now known as Parkinson's disease. It has a prevalence of 0.3% in the entire population, 1% in those over 60 years, and an estimated incidence of 8-18 per 100,000 every year (de Lau & Breteler, 2006). The incidence of PD increases with age. The median age of onset for all forms of Parkinsonian syndromes is 61.6 years, with median idiopathic PD onset at 62.4 years. Onset before age 30 is rare, though up to 10% of cases of idiopathic PD begin by age 40 (Dorsey et al, 2007). Better healthcare management has led to an increase in the aging population all over the world, as a result of which the incidence and prevalence of PD is set to increase over the coming years.

Parkinson's Disease (PD) is a chronic neurodegeneratve disorder in which there is loss of dopaminergic nigrostriatal neurons of the SNPc , an important projection nucleus of the basal ganglia. This loss of neurons is also coupled with intracytoplasmic inclusions known as Lewy bodies.

As discussed earlier, the loss in dopaminergic input from the SNPc, decreases the activity through the direct pathway, since the SNPc along with the cortex, excites the striatum, which in turn inhibits the GPi leading to disinhibition of the thalamus. The net increase in activity from the indirect pathway, which is excitatory to the GPi and inhibits the thalamus, causes decrease in movement, a state of hypokinesia. Loss of further spatial and temporal focus of GPi activity, along with abnormal synchrony of GPi neuronal discharge occurs due to loss of dopamine. Disinhibition of both desired and undesired motor patterns lead to abnormal movements.

The cardinal features of PD are tremor, which may become progressive, bradykinesia and rigidity. The neuronal loss occurs beyond the dopaminergic system, the patient may also have autonomic, attentional and cognitive deficits as the basal ganglia are connected to the amygdala and hippocampus. Symptomatic PD occurs usually after about 60 % of the dopaminergic neurons of the substantia nigra have degenerated.

The pathophysiology of PD includes the degeneration of nigrostriatal neurons along with the formation of Lewy bodies due to intraneuronal inclusions, which are eosinophilic cytoplasmic aggregates, which may include alpha synuclein, parkin, ubiquitin and neurofilaments.

2.2 Etiology and genetics

Etiology of almost all cases of PD is unknown. Since, in more than 90% of the cases, PD arises as a sporadic condition i.e, in the absence of any apparent genetic linkages. A few decades ago, MPTP (1 – Methyl – 4- phenyl -1,2,3, 6 – tetrhydropyridine) usage in drug abusers led to an understanding of brain damage due to toxins. Damage to the nigrostriatal dopamine pathway was noted. Since then most etiologic theories of PD involve genetic as well as environmental factors (Jankovic & Tolosa, 2008)

However, genetics is yet to play a definitive part in IPD cases, though mutations in Parkin, Ubiquitin C – terminal hydrolase L1 (UCH – L1), PINK1 and LLRK2 genes have been identified in familial Parkinson's. PINK1 and LLRK2 mutations have also been found in those without family history too.

Gene	Name/ Locus	Clinical features/ forms	Type /Occurrence
Parkin	PARK2 /chromosome 6	Early onset PD with loss of SN neurons	Recessive/Common cause of early PD
PINK1	PARK6/ Chromosome 1	Early Onset with mitochondrial dysfunction and oxidative stress	Recessive/ Less common
LLRK2 (leucine repeat rick kinase 2)	PARK8/chromosome 12	Typical IPD with variable tau pathology)	Dominant/ Most common
Alpha – synuclein	PARK1/chromosome 4	IPD or demetia with Lewy bodies	Dominant/Rare

Table 2.1 Genes linked with the occurrence of PD Genetic association seen in some cases of PD. (Sources: Parkinson' s disease and movement disorders, Zaranz JJ et al, 2004, Zimprich et al, 2004, Lucking CB et al, 2000, Valente et al, 2004, Hatano et al, 2004, Rogaeva et al, 2004, Vila & Przedborski, 2004)

2.3 Signs and symptoms of PD

The assessment of PD involves the identification of the cardinal features of PD namely, rigidity, tremor, akinesia or hypokinesia and postural instability. Tremor associated with PD is known as rest tremor as it is present whilst the person is at rest, when the muscles are relaxed, and it may disappear on movement. Freezing of gait, and the appearance of a mask-like expression are other hallmarks of PD. Non-motor features include autonomic dysfunction leading to constipation, orthostatic dysfunction, and neuropsychiatric symptoms such as depression, dementia, psychosis and cognitive decline. Other symptoms include sexual dysfunction, namely an increased or pathological sex drive, excessive saliva, gambling tendencies, micrographia and impairment of fine motor skills and co-ordination, difficulty with speech or slurred speech or difficulty swallowing.

2.4 Clinical assessment of PD

It involves both the identification of the signs and symptoms of PD (all of which may or may not be present) and distinguishing it from other forms of Parkinsonism namely progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, and drug induced Parkinsonism among others.

Assessment is made by a thorough neurological examination, with correlation of clinical history especially in relation to performing fine motor tasks of daily activity. Screening tools such as the Unified Parkinson's Disease Rating Scale (UPDRS) and the Modified Hoehn and Yahr (HY) staging are used in the clinical setting. The H & Y rating is between 1 and 5, with 4 and 5 representing the late or advanced stages of the disease and 1 and 2 being at the lower end of the spectrum. The UPDRS was the main screening tool in our study and it includes these sections:

1. Mentation, mood, behavior
2. Other activities of daily living
3. Motor scoring by the clinician
4. Complications of therapy
5. H and Y staging
6. Part VI - Schwab and England Activities of Daily Living scale

Other assessments include the MMSE (Mini Mental Status Examination).

Each sign or symptom under every section can have a score between 0 – 4. The scoring up to Part 3 gives a maximum of 176 for 31 questions.

2.5 Treatment modalities

Treatment includes both pharmacological and surgical methods. The principle behind treatment is to facilitate dopaminergic transmission. Pharmacological methods include administration of L–dopa, COMT (Catechol-O–methytransferase) inhibitors such as entacapone which prolong the plasma levels of L –dopa, dopamine agonists like bromocriptine, pramipexole and ropinrole, MAO – B inhibitors such as selegiline, which inhibit the deamination of dopamine and thereby prolong its half–life and anticholinergic medications like trihexyphenidyl, which provide an anticholinergic effect on the striatum which improves symptoms by achieving a closer balance of dopamine levels. Pharmacological treatment may include a well-regulated dosage of one of more of the drugs from the above classes on the basis of the stage of the disease, and type of symptoms.

Surgical treatment due to the waning of pharmacological treatment due to the progression of disease includes Deep Brain Stimulation (DBS) or pallidotomy, subthalamotomy or thalamotomy. Though the mechanism of ameliorative affects of pallidotomy is not completely understood, it has been attributed to the reduction of excessive inhibitory outflow from the GPi (Jahanshahi et al, 1995) by lesioning the posteroventral pallidum. DBS is considered to be a more effective, non –ablative therapeutic approach. Though the mechanism is not completely understood, it is understood that chronic high frequency stimulation in patients with PD is therapeutic as it changes the irregular, abnormal basal

ganglia output to the cortex to a more regular and better tolerated pattern (Kandel (2012): Principles of Neural Science, Krauss et al, 2001: Surgery for Parkinson's disease, p 138, Edition 1), and has been the choice of treatment in recent years. The specific surgical treatment would be based on the type of predominant symptom.

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2.6 Parkinson's disease: Why we need more research?

1. PD follows a progressive course over a decade or more, corresponding to ongoing neuronal loss, particularly in the substantia nigra. There is a preclinical phase of uncertain duration, probably about 5 years (Morrish et al, 1996), during which there is a progressive loss of dopaminergic neurons until the threshold for clinical symptoms is reached. Clinical manifestation of PD usually appears after approximately 60% of the dopaminergic nigral cells have been lost (Fearnley, 1991).

2. Disease modifying strategies by way of putative neuroprotective therapies (Ravina et al, 2003, Nichols et al, 2009) are being studied. However, to study their efficacy as treatment or postponement of disability, it is imperative that we have definitive clinical end points for the disease (Löhle et al, 2010). We have crude estimates in terms of the time needed for PD patients to reach designated end points such as the need for dopaminergic therapy, postural instability, dyskinesia and motor fluctuations (Jankovic & Tolosa, 2007). However, there is a need to establish clear, valid measurements of progressive impairment to assess prognosis of the disease, as well as begin or alter any form of therapy, as the ones in current use are arbitrarily chosen or are based on clinical experience. An objective measure for these endpoints would be more helpful in strategizing or formulating the treatment plan.

3. Idiopathic Parkinson's disease (IPD) is strikingly similar to other Parksinsonian conditions such as multiple system atrophy, progressive supranuclear palsy, essential tremor, frontotemporal dementia (FTD) and cortico-basal degeneration (CBD)(Galvin et al, 2001, Burn & Lees, 2002). Therefore, practical, sensitive and objective methods to be able to distinguish between IPD (the form of PD seen in majority of the patients) or sporadic PD and other forms of Parkinsonism are necessary.

4. Objective methods, which can help stratify PD into its subtypes on the basis of performance, may help with strategizing therapy (if there is a correlation between subtypes and type of treatment modality).

5. Rating scales such as the UPDRS and the H & Y staging alone are not objective enough to provide clear end points (Movement Disorder Society Task Force on Rating Scales for Parkinson's disease, 2003). There are many methods to assess the presence of IPD, and study its progression. However, we are yet to identify one method, which has sufficient objectivity to provide a reasonable amount of accuracy. These methods will be discussed in the next section.

Chapter 3

Huntington's disease

3.1Etiology and Genetics

Huntington's disease is an autosomal dominant, fully penetrant neurodegenerative disorder. It was first described by George Huntington (Huntington G, 1892) and was subsequently called Huntington's Chorea. Its etiology is due to an expanded CAG trinucleotide repeat seen in the Huntingtin gene (IT15) on chromosome 4 (The Huntington's Disease Collaborative Research Group, 1993), which codes for the *huntingtin* protein.

Huntington's Disease (HD) though shows a worldwide prevalence ranging from 2-10 per 100,000 (Pringsheim et al, 2012). It has a stable prevalence of 5-10 per 100,000 in Caucasian populations (Francis O Walker, 2007, Rubinsztein, 2002). HD has a wide range of onset from infancy to 80 years, prior to which the individuals do not have any detectable clinical abnormality (Myers RH, 2004).

3.2 Clinical features and pathophysiology

HD is a movement disorder, which comprises progressive motor dysfunction with affective and cognitive changes along with changes in behavioral patterns. Clinical manifestation is in the form of involuntary movements such as chorea and dystonia, bradykinesia, incoordination, progressive cognitive decline, and behavioral abnormalities in the form of depression and psychosis, due to selective neuronal loss in the striatum.

As described under motor loops, Huntington's is a basal ganglia disorder. The mechanism of disease is via the atrophy or degeneration of the caudate nucleus, which is caused by the intraneuronal inclusions aggregates formed by the Huntingtin protein. This degeneration of part of the striatum, leads to a decreased output through the indirect pathway, as the striatum no longer inhibits the STN, which disinhibits the thalamus. As there is no inhibitory influence on the VL nucleus of the thalamus by this indirect pathway, these neurons in the VLN cause motor abnormalities by firing without control, in a random manner cause hyperkinesia and disrupt voluntary movement, even if desired (Kandel, 2012: *Principles of Neuroscience*, Bear & Connors (2007): *Exploring the brain*).

3.3 CAG repeat size and disease severity

HD is a dominant disorder and hence requires only one HD allele for the development of the disease; however, its progression depends on the number of CAG repeats present on the allele. CAG repeats show good correlation with the severity of the disease along with confirming its presence. CAG repeat of 40 and above is definitive of severe HD. Hence it is described as fully penetrant, as the individual will develop the disease, though the time of its development cannot be predicted accurately. 36 repeats and above confirms its presence (reduced penetrance), which implies some may develop the disease and some may not, 27 – 35 is considered to be at intermediate risk (no reported cases). The largest CAG repeat length, at which no pathology is expected to develop, is 35.5 (John et al, 1997). 26 and fewer are deemed to be a normal number of repeats and the individual has no risk of developing the disease. The majority of HD patients have pathological repeat sizes in the range of 40 – 45 (Snell et al, 1993; Duyao et al, 1993) and therefore are fully penetrant.

CAG expansion can provide an estimate of disease onset albeit only for about 50 % of those identified to possess the faulty gene (Andrew et al, 1993; Snell et al, 1993; Duyao et al, 1993). However, when the repeats run in the family, the age of onset is earlier with each succeeding generation (Duyao et al, 1993; Kremer, et al, 1994; Andrew et al, 1993).

The number of CAG repeats helps in predicting the age of onset of the disease, as it determines the degree of neuropathological changes occurring in the striatum (John et al, 1997). Striatal dysfunction in HD is given by

Striatal Dysfunction = Constant x Age x (CAG – 35.5)

The CAG repeat size is also an indirect measure of scoring the disease burden known as DBS (Disease burden score) and has been used to study progression of HD.DBS = (CAG Repeat – 35. 5) x Age (Penney et al, 1997;Tabrizi et al, 2009).

3.4 Clinical Diagnosis and screening

Diagnosis is undertaken through testing for CAG repeats along with careful clinical examination. Screening for HD maybe performed when there is direct family history of HD, even in the absence of symptoms, after genetic counseling. HD patients have a healthy period followed by a pre-symptomatic phase, after which overt clinical manifestation occurs. The pre-symptomatic phase is linked to subtle changes in personality, motor control and cognition, which are not noticeable to the patients themselves (Snowden et al, 1998, Paulsen et al, 2008). Hence, HD comprises of pre-manifest gene carriers, in whom there are no clinical signs or symptoms though the faulty gene is present, and manifest individuals in whom clinical signs are present. These two groups can be separated even if there are subtle changes in both groups, by using the DBS as described above.

Clinical diagnosis is possible by the identification of clinical features such as hyperkinesia in the form of chorea or dystonia, incoordination, saccadic changes and behavioral abnormalities along with cognitive dysfunction. Clinical assessment using a complete neurological examination is augmented by using scoring methods such as the Unified Huntington's Disease Rating Scale (UHDRS).

The UHDRS is used for scoring individuals with signs of the disease or pre-symptomatic HD patients. It tests the motor, executive, behavioral dysfunction and functional ability (Huntington Study Group, 1996). The motor component of the UHDRS is commonly used to assess prognosis. It consists of 31 items, with a rating between 0 to 4, with 4 representing severe impairment, and 0 indicating no impairment or abnormality. It has a maximum total score of 124. Similar to PD, the MMSE can also be used to assess the individual. The components of the UHDRS are:

1. Motor Assessment
2. Cognitive Assessment
3. Behavioral Assessment
4. Independence Scale
5. Functional Assessment
6. Total Functional Capacity (TFC)

The Total Functional Capacity Scale is particularly useful in delineating the stages of the disease. It scores the individuals abilities in the areas of occupation, finance, chores, activity of daily living and care level from 0 – 2, with 0 denoting inability to perform these activities without help. The total helps to stage the individuals from Stage 1 to V (Balmford & Shoulson, 1989, The Huntington Study Group, 1996).

TFC

Score	Stage
11- 13	I
7 -10	II
3 - 6	III
1 - 2	IV
0	V

Table 3.1 Total functional capacity scoring in stages of HD. Greater disease severity or later stages of the disease are denoted by lower TFC scores.

3.5 Treatment modalities

HD has no specific treatment modality that targets the accumulation of the huntingtin protein and the neurodegeneration it causes. Treatment in HD is therefore, symptomatic and entails treating chorea, and psychiatric symptoms such as depression, anxiety, psychosis and sleep disorders.

In the early stages atypical neuroleptics such as clozapine, may be administered along with symptomatic treatment for neuropsychiatric symptoms. At later stages, neuroleptics and antidepressants may be used (Thomas et al, 2004). Supportive therapy in the form of psychological counseling, group therapy, physical exercises, dietary changes serve as adjuncts, albeit they do little to alleviate symptoms. Pharmacological trials to identify treatments for HD, though unsuccessful, include drugs to prevent of accumulation of the huntingtin protein (Hersch et al, 2003), along with gene therapy to change the faulty gene itself (Bloch et al, 2004).

3.6 Huntington's Disease: Why we need more research?

1. The presence of the huntington gene implies the eventual development of the disease, however, its age of onset is not accurately predictable.

2. Disease progression in the manifest group of HD (MG) cannot be objectively measured. UHDRS and TFC provide numerical scores, however, they are subject to examiner error.

3. Though an effective therapy has not yet been definitively identified to slow or delay the onset of HD, recent clinical trials have shown promise in the direction of slowing progression of the disease (Gardian, et al, 2004). However, since standardized, validated clinical end points in the disease have not been identified, either during the pre or symptomatic phase, the ability to show evidence of efficacy of disease modifying therapies is reduced (Mestre et al, 2009, 2012).

4. Studies which have analyzed eye movements among pre manifest gene carriers of HD (PMG) and manifest HD (MHD) patients, have shown significant differences (Kirkwood et al 2000, Langbehn et al, 2007). Other studies involving motor response in the form of hand tapping or finger tapping have also shown significant differences between PMG and MG (Sanchez et al, 1999, Rowe et al, 2010, O'Keeffe et al, 2007, Bechtel et al, 2010).

   However, we are yet to identify a really reliable method (also known as biomarkers) that would provide an objective measure, which is reproducible and sensitive among the different groups of HD, namely pre manifest (PMHD) gene carriers, early and the late stage manifest group (MHD).

Chapter 4

Biomarkers

4.1 Biomarkers: Definition, types and validation

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention. In PD and HD, the centers of pathology are deep-seated, and not easily accessible. It is further complicated by the incomplete understanding of the correlation between neuropathological change and clinical expression in these particular disorders, and therefore biomarkers, which have been validated, could prove useful.

A surrogate marker is one that is intended to substitute for a clinical end point. A surrogate end point is expected to predict clinical benefit (or harm or lack of benefit) based on epidemiological, therapeutic, pathophysiological or other scientific evidence. They are a subset of biomarkers (Biomarkers Definition Working Group, 1993).

Therefore a biomarker objectively either helps in predicting disease onset, detecting the disease, tracking its progression. Even surrogate markers help in demonstrating the clinical efficacy of the new treatment in place. The use of certain biomarkers maybe used to detect the presence of a disease, and thereby exclude the presence of the other.

The accuracy of a biomarker is determined by its sensitivity, which is the proportion of patients with the disease who are identified by the test and its specificity, which is the proportion of patients without the disease who are excluded by the test. Therefore, a biomarker with a high positive predictive value will help in identifying the disease and a test with a high negative value will be very good at excluding the disease (Eller & Williams, 2009).

Identifying biomarkers also helps us to have a standardized system of disease evaluation, which should expedite the process of achieving breakthroughs in HD and PD research.

4.2 Characteristics of a good biomarker:

1. Results should be reproducible and consistent
2. Sensitive
3. Specific
4. Easy to use
5. Cost effective

4.3 Types of biomarkers

There are many biomarkers of potential use for the various aspects of the two disorders in question. However, though not comprehensive, we shall classify them into four broad categories:

1. **Clinical biomarkers**

1.Depression scales
2.Oculomotor biomarkers (Saccadometry)
3.Vision
4.Olfaction
5.Hand tapping/Finger Tapping
6.Surface EMG & Long latency stretch reflexes
7. Grip Force, Actigraphy(HD)
8. Cognitive/psychological tests & CANTAB/mobile cognitive testing.
9. Gait analysis (HD)
10. Graphimetry

2. **Imaging**

1.PET & SPECT
2.MRI
3.Cardiac MIBG scintigraphy
4.Transcranial ultrasound
5. DTI (HD)
6. MRS (HD)

3. Biological fluid biomarkers

1.α – synuclein in CSF
2.Tau forms – CSF
3.$A\beta_{42}$ in CSF
4.Proteomic profile – CSF
5.α – synuclein in plasma
6.Metabolomic profile – Plasma
7.Oxidative stress- Hydroxy-2'-deoxyguanosine, Malondialdehyde, GPx (HD)
9. Metabolic, transcriptomic, inflammatory proteins (HD)
10. Endocrine markers – Cortisol, Ghrelin, Leptin, CART (HD)

4. Genetic testing

1.CAG Repeats in the htt gene, to identify presence of the disease and indirectly calculate disease onset and progression (HD)
2. Recessive mutations in PINK1 gene (PD)
3. LLRK, PARK2, PARK6, PARK8

(*Antoniades et al, 2008, Eller & Williams, 2009, O'Keeffe et al, 2009, Shaw et al, 2007)*

UHDRS and UPDRS are not included in the above as they are not objective.

4.4 Clinical Biomarkers:

Clinical rating scales like the UHDRS in HD, UPDRS and H&Y scales in PD are the standards used at present to assess disease progression. While they are helpful, these are susceptible to inter-rater variability, which contributes to error. Along with the imperfect ability of subjective motor measures to capture disease progression, it makes these scales unreliable.

Clinical biomarkers are of special value in PD and HD, as the motor phenotype is the standard method for the clinical assessment of PD and HD. Hence, automated techniques aimed at detecting subtle motor abnormalities earlier in pre-manifest HD, and thereby shorten the pre manifest period, along with increasing the reliability of motor measures in staging manifest disease are being investigated. These automated techniques may help distinguishing between forms of parkinsonism and the stage of PD in an objective manner. However, the clinical tool is an especially valuable biomarker when it correlates with disease presence and progression. Among clinical biomarkers outlined above, hand tapping has been particularly studied in HD and PD due to its ease of use, and easy access in the clinical environment.

Chapter 5

Hand/ Finger tapping

5.1 Introduction

Hand/finger tapping has been investigated as a possible biomarker in PD and HD in recent years. It involves testing the motor response in the execution of simple repetitive, well-learned, sequential finger movements of varying lengths and self selected movements.

The term hand and finger tapping have been used synonymously in studies, though hand tapping in some cases refers to pronation, supination movements of the hand, whereas finger tapping generally refers to repetitive movements, which can be paced, self-paced or sequential. Though the terms are somewhat loosely used in reported studies, it is necessary to distinguish between the HT (Hand tapping) and FT (finger tapping), as they are different types of movement, and therefore may or may not both be impaired.

Common tapping tasks include tapping with the index finger of the dominant or non-dominant hands or both, on specified targets in self paced, externally paced (via auditory or visual cues), sequential movements between different targets, or hand tapping tasks by way of pronation and supination movements on a recording surface. The index finger is most commonly used for performing single finger tasks, as it has a better dynamic motor function in comparison with the middle finger (Aoki et al, 2001) and is more practiced in performing fine motor actions. This is primarily because the index finger is crucial for fine, motor tasks and well trained, minimizing the potential impact of motor learning (*Bechtel, 2010).*

Sex differences in finger tapping tasks have not been shown in PD or HD (Antoniades et al, 2010), though a study in normal children showed girls performed better in speeded tapping tasks, and maintained rhythm consistently in externally paced tasks (Wolff et al, 1976).

The effect of age is a factor to be considered in tapping. The effect of age shows some mixed findings, while some studies show a significant difference (Cousins et al, 1997,Critchley, 1956,Mortimer et al, 1988, Saft et al, 2006, Jimenez-Jimenez et al, 2011) others show no difference in tapping patterns if the tasks are based on fine motor skill and if the influence of learning has been eliminated by practice (McCullogh et al, 1996, Jackson et al, 1995). While bradykinesia or akinesia is a hallmark of PD, motor slowing is considered to be present in an aging population (Bornstein et al, 1985, Hakkiken et al, 1996, Moehle et al,

1989). It is important to separate motor aging from the bradykinesia of movement disorders, both by eliminating the learning element, and by increasing the complexity of tasks, which will elucidate the difference in impairment in voluntary movement in PD and aging.

As tapping with single and double fingers use different strategies (Aoki et al, 2001), which is evidenced by impairment in the two finger task in HD more often than PD (Refer Tables 5.1 & 5.2). Most studies however, involve single finger tapping, and a few involve double finger tapping. Studies with double and single finger tapping have shown significant differences in control populations (Aoki et al, 2001), which has been attributed to the higher spatial complexity that double finger tapping involves (Gordon et al, 1998).

Analysis of movement sequences in tapping arise from both anticipatory motion and coupling of fingers to perform fine motor tasks in normal individuals, and trained musicians (Loehr & Palmer, 2007) which documents the relationship between tapping and anticipatory motion to perform a fine motor task, which is precisely impaired in PD.

Tapping is a voluntary task, involving fine motor skills, which is enabled by the action of the basal ganglia as part of the motor loop, as explained earlier. Studying the impairment in performing one of the simplest, voluntary actions gives us a measure of a movement disorder. Though other conditions such as

essential tremor or anxiety disorder may affect the individual's ability to tap, it can be ruled out by performing different types of finger tapping tasks, measuring the frequency of tremor and by other clinical features. Other tapping parameters, change such as force change to a different extent in these disorders (Bechtel et al, 2010, Aoki et al, 2001).

Impairment of finger tapping in HD and PD is apparent clinically, and is further attested by imaging during tapping tasks. Hand tapping studies in control populations have been studied to identify the focal areas of activation, during different types of finger tapping tasks. Voxel–wise, co-ordinate based meta analysis performed on 685 sets of activation foci gathered from 38 studies employing hand tapping tasks in normal subjects has shown robust concordance with bilateral sensorimotor cortices, SMA, left ventral pre motor cortex, bilateral inferior parietal cortices and bilateral basal ganglia. Auditory and self paced tasks shared greater concordance with the bilateral claustrum, and visually paced groups with the bilateral insula (Witt et al, 2008), which corresponds with data demonstrating a relationship between impaired performance in finger tapping and the presence of basal ganglia disorders such as PD or HD.

5.2 Types of tapping tasks

The simplest type of finger tapping task is based on the rate of tapping. The number of taps performed in a specified amount of time. Self-paced tapping is tapping at the individual's own pace (fastest usually), which may or may not be timed, and externally paced (which maybe be through the flashing of a light or by playing a sound), or internally paced (by asking the patient to tap at a certain interval).

Other types of finger tapping tasks are based on simple and complex reaction time. Simple reaction time analyses response time to a stimulus, while complex reaction time, is a choice stimulus, which involves voluntary movement, and learning. Voluntary control and procedural learning can be studied by moving from simple to complex reaction time tasks, and these have been shown to be impaired in HD (Knopman & Nissen, 1991) and PD (Pastor et al, 1991, Jahanshi et al, 1992, 1993). Some devices measure only tapping rates and inter-tap intervals, (Fig 5.1) and some measure reaction time, but not both.

A literature review follows based on my search of all tapping and reaction time tasks, which involve hand or finger tapping in PD and HD. I did a comprehensive search using terms such as 'tapping tasks in PD, finger tapping, hand tapping, reaction time in PD, and similarly HD on Google, Pubmed and using references from other papers.

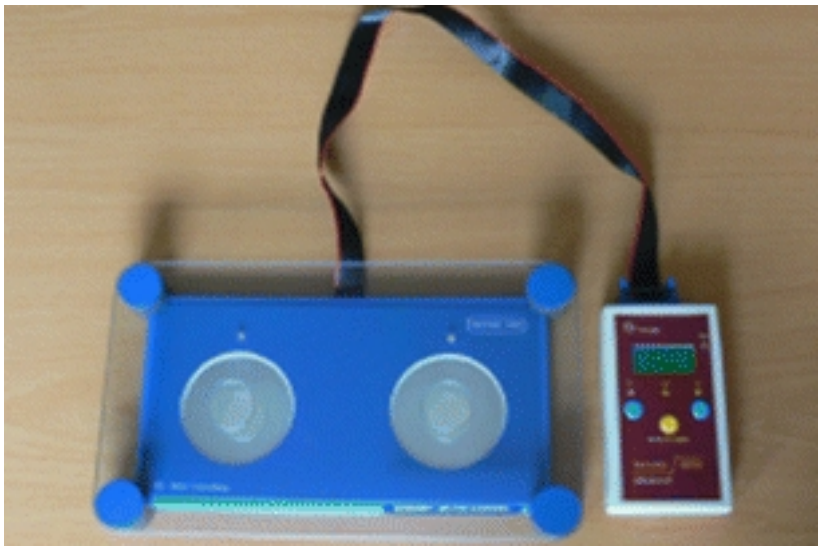


Fig 5.1 **Ober hand tapping device** used to measure tapping rates and inter tap intervals only in PD and HD. (Source: Antoniades et al, 2012)

Table 5.1
Tapping and reaction time studies in Parkinson's disease: A review of hand/finger tapping studies measuring various parameters in PD.

	Test	Author/ Year	Result	Implication
1.	Movement between two points in 30 s	Macleod et al, 2010	PD patients tapped 10 % less than controls, 18 -74 taps	Movement between points is longer in PD, and reference age established.
2.	Repetitive, externally cued 550 ms	O'boyle et al, 1996	Total variance of the inter-response interval (IRI) was higher in PD than controls	TV of IRI was higher in the 'off' medication condition, and only CV was different in the 'on' condition.
3.	Time reproduction task, external cue presented, and internally paced tapping had to be performed	Jones et al, 2008	Mean time to tap at an internal pace was more variable in PD than controls as the CV was higher at 1000ms	Internal pace is affected at 1000 ms.
4.	Long sequential finger movements – 6 tasks	Catalan et al, 1999	Complex finger movements showed differences in rCBF in PD and controls.	PD patients showed increase in SMA and cingulate along with areas activated in controls
5.	Single and double and double finger repetitive tapping	Haaxma et al, 2010	Single tap $p<0.02$ Double tap $p<0.001$	PD patients performed worse than controls in alternative double and single target tapping.
6.	Self paced, fastest pace, metronome/external cue	Yahalom et al, 2003	Fastest pace $p<0.01$ Tremor predominant group $p<0.05$ in metronome based tapping	PD patients performed worse in self paced tasks, and tremor predominant group performed worse in the externally cued

				task.
8.	Alternative finger tapping	Pal et al, 2001	Single and alternate finger tapping on adjacent keys (F1K1, F2K2) – p <0.001	Alternate finger tapping is slower in PD patients and correlates with PET imaging
9.	Tapping, externally paced followed by internally paced	Duchek et al, 1994	P <0.07 in PD versus controls for IRI (Inter Response Interval)	No difference in PD and controls in IRI.
10.	Alternate tapping on adjacent targets in 45s, fast paced	Antoniades et al, 2012	P <0.01 in PD versus controls	PD performed worse in alternate finger tapping.
11.	Alternate tapping between two points	Ruiz et al, 2007	P <0.0001 in PD versus controls	PD performed worse in alternate finger tapping indicating poor motor performance.
12.	Alternate finger tapping	Tavares et al, 2005	Correlation of tapping scores with UPDRS scores over 9.5 months	QDG score from the tapping task correlates with UPDRS
13.	Speeded tapping for 60 s of thumb and forefinger with sensors and accelerometer attached with UHDRS finger taps	Yokoe et al, 2006	Amplitude (distance between fingers before touching) decreased with increasing UPDRS taps score, SD of IRI for irregularity of rhythm increased with increasing UHDRS taps score,velocity of taps decreased with increasing UPDRS score	Motor variability increases with a higher UPDRS, and as amplitude and velocity decrease, bradykinesia is increasingly measured in patients with higher UPDRS scores.
14.	Speeded tapping for 60 s of the thumb and forefingers using an accelerometer attached with touch sensors on the	M. Yokoe et al, 2009	Mean of Velocity of each tap, mean amplitude (distance moved between fingers before touching), and SD of IRI (Inter	Mean of velocity of tap was found to be the best to pick up significant difference in the PD patient in

	fingers and comparison with UHDRS		rate interval), and IRI as mentioned in the previous study	tandem with the UHDRS scores. It is the best parameter showing the closest relationship to UPDRS scores.
15.	Self paced, and metronome paced (externally cued)	Bazner et al, 2005	Variability of amplitude, frequency and angular velocity, $p < 0.01$	PD performed worse in self-paced and externally paced tasks.
16.	Finger tapping, reaction time tasks to test executive functioning and neurocognitive speed	Frias et al, 2007	PD patients were slow in the reaction time tasks, and inconsistent with the most complex reaction time task	Executive functioning and Neurocognitive speed may be good clinical markers in PD
18.	Externally paced tapping to an auditory cue from 1 to 7 HZ	Nakamura et al, 1978	PD patients tapped at 5 to 6 Hz at a critical frequency of 2.5 to 5 Hz	They described this as a hastening phenomenon due to a release in intrinsic oscillation at the critical frequency which is masked in normal subjects
20.	Fast paced tapping	Arias et al, 2012	Frequency of tapping and time and duration of fatigue was analyzed	Fast paced tapping is not an objective marker in PD as it is confounded by fatigue
21.	Isometric force measurement	Stelmach et al, 1989	Peak force was almost the same in PD, $p < 0.05$	Ability to apply force was not lost, albeit the duration was not sustained.
22.	Simple and Choice reaction time tasks	Kutukcu et al, 1999a	Simple (SRT) and Choice (CRT) were delayed in PD, $p < 0.001$	PD patients took longer in performing voluntary movements as SRT and CRT.

23.	Simple and choice reaction time tasks	Jahanshi et al, 1992	SRT and CRT were delayed in PD, mean was calculated using values of both hands	Voluntary movements were longer in PD, with CRT having higher delays.
24.	Simple and choice reaction task	Smith et al, 2007	SRT and CRT on the basis of auditory and visual cues. The stimulus duration was long and short. SRT and CRT were prolonged in PD, but only when it was a long duration stimulus	The specific long duration impairment in PD, may demonstrate the role of the basal ganglia in the disturbance of the internal clock.
25.	Serial reaction time task	Jackson et al, 1995	SRT (Serial Reaction time) was prolonged, $p < 0.01$, but variability of SRT did not show a significant difference	The last few trials, showed a decrease in SRT, which could imply a learning effect. As variability was not consistent, it may reflect a disruption in rhythm even in there was no deficit in learning the temporal order information.
26.	Simple and 2 and 3 choice reaction time tasks (2-CRT, 3 – CRT)	Kutukcu et al, 1999b	SRT, 2 – CRT, 3-CRT in the 1000 Hz cue, $p < 0.001$, Response time was most delayed in 3 – CRT, the difference in the performance of the left and right hand was almost the same in PD unlike the controls, $p<0.0001$	Increasing the complexity of the task, maybe more helpful in separating PD. Since both hands seem to perform equally worse, using only the dominant hand in bilateral PD is an option.

27.	Simple Reaction time tasks	Deroost et al, 2006	Patients were divided into subgroups, PD- fast and PD- slow. PD – fast. Learning effect of the sequence was absent in the slow group. RTs were slower in the slow group, but both remained variable to a similar extent	Sub grouping revealed that the sub types maybe divided on the basis of the response time, and maybe pathognomic of the different types (if any) of neuropathological change occurring.
28.	Four finger tapping, paced and un-paced	Muir et al, 1995	Hastening was observed, but was not exclusive to PD. Frequency at which PD patients lost synchrony was 2.6 Hz vs 4.6 Hz in controls. Tapping variability was not significantly different.	PD patients were slower than controls, showed hastening more often, and had a limiting frequency beyond which synchrony was lost, which demonstrates dysrhythmicity and bradykinesia.
29.	Simple reaction tasks were studied with fMRI imaging. Rule/sequence learning in SRT in early PD vs controls a. During Pre training b. During Imaging	Werheid et al, 2003	RT across both groups, $p < 0.05$. Pre training period- PD did not show lower RTs in the end versus controls, but had lower RTs at the end during the actual imaging session RTs in random blocks were slower than in sequences. Striatal activation was seen in PD but not controls in sequence SRTs	In early PD, with lateral dopaminergic projections being affected, medial dopaminergic connections may help keep learning intact by the differences in activation during pre training and imaging.

30.	Simple and Choice reaction tasks with auditory cues	Pastor et al, 1992	Tapping, simple reaction time and movement time, $p<0.05$, absolute errors were higher in PD under all conditions. Administration of L-dopa decreased errors, and even at faster frequencies of 5 Hz and 3.3. Hz.	Time estimation is abnormal in PD as the internal clock is disturbed, as evidenced by the inability to reproduce timing tasks without errors.

Table 5.2

Tapping and reaction time studies in Huntington's disease: A review of hand/finger tapping studies measuring various parameters in HD.

No.	Test Group	Test	Author/Year	Result	Conclusion
1.	Early, late HD, Controls and Pre symptomatic gene carriers	Speeded and Metronome based task	Bechtel et al, 2011	P<0.001 across all groups, late and early MG and controls	Tapping deficits are evident throughout manifest and pre-manifest stages.
2.	Early, late HD and controls	1.Speeded tapping in 30 seconds 2. Variability in tapping rhythm	Michell et al, 2008	P <0.001 for taps in 30 seconds, variability of taps, p <0.016 r = -0.49 correlation with motor UHDRS	Difference in early HD, late HD and controls correlates with UHDRS
3.	Pre-symptomatic gene Carriers of HD (PMG)	Speeded tapping, Auditory reaction time, visual reaction time and decision time	Kirkwood et al, 2000	P <0.05 in reaction time and tapping, though the variability was less	Subtle motor changes can be detected through tapping and reaction time tasks.
4.	PMGs, early HD and controls	Self paced/ speeded tapping, force transducers	Tabrizi et al, 2009 (TRACK HD)	PMG vs controls, p < 0.001, HD vs controls, p <0.001	Pre manifest and Manifest HD had lower tapping rates.
7.	PMG vs non gene carrying controls	Probability of diagnosis with UHDRS motor scores and finger	Biglan et al, 2009	Finger tapping and probability of diagnosis, p <0.001	Tapping performance correlates with probability of developing manifest HD.

		tapping			
8.	Early and mid HD (as defined by authors) vs controls	Simple Reaction time	Knopman et al, 1991	SRT, p <0.004	SRT was delayed in early and mid HD
9.	PMG, MG and controls over 3 years	Alternate finger tapping over 45 s	Antoniades et al, 2010	Finger taps mean scores, p <0.01 between PMG and MG	Tapping rates were lower in MG, and decreased over 3 years.
10.	Early HD, cross sectional study	Speeded tapping and PET imaging (raclopride binding)	Sanchez-Pernaute et al, 2000	TFC correlation with CAGxage (r =0.956; p <0.001)	Finger tapping shows positive correlation with striatal (D2) loss.
11.	Early HD, PMG and controls	Force transducer based speeded, and metronome tapping	Bechtel et al, 2010	All tapping intervals correlated with the UHDRS	Controls performed better than PMG and MG in fine motor tasks.
12.	PMG with no functional decline	Speeded tapping, tapping to an external cue followed by internal pace	Langbehn & Paulsen, 2007 (PREDICT – HD)	Tapping rate and years to diagnosis, p <0.001	Decrease in tapping performance/rate as the years to diagnosis decreased.
13.	PMG, MG and controls	Tapping rate in speeded tapping for 32 seconds on a computerized target	Saft et al, 2006	Tapping rates were lower across all groups of HD vs controls (p<0.001)	Decrease in motor performance through tapping rate was observed in both MG, and PMG versus controls.
14.	MG and controls	Pronation-Supination, tapping between two points	Ruiz et al, 2002	Relation between TFC and time between two points, r = -0.845, p<0.0001	Finger tapping between two points can detect deterioration over time.

15.	PMG, MG and controls	Alternating hand positions	Snowden et al, 2002	Hand tapping within the different groups, p <0.005	Tapping performance is linear with disease progression in HD.
16.	PMG, MG and controls	Speeded tapping, reaction time,	Hefter et al, 1987	RT, p <0.01, in some groups	Reaction times were varied, some slower, and some same as normal.
17.	HD patients vs controls	Total motor score of UHDRS	Mahant et al, 2003	Modified motor score and age at onset, p <0.001	Motor scores correlate with disease progression.
18.	PMG, follow up for 10 years	Auditory and visual reaction time, speeded and alternate tapping	Solomon et al, 2008	Auditory reaction time (-0.56), Visual reaction time (-0.42), movement time (-0.4), finger tapping of button (-0.36)	Response time and finger tapping parameters correlated with estimated age of onset, during two visits over 10 years showing a relationship in quantifiable motor decline before disease onset.
19.	PMG and non gene carrier controls	Rapid alternating movements	Kirkwood et al, 1999	Rapid alternating movements declined more rapidly among PMG vs non-gene carrier controls, p <0.005. Follow up examinations revealed the same results.	Regular standardized assessment of motor decline in PMGs may help in monitoring disease progression.

20.	Double blind PMG and non gene carrier controls and MG	Alternate target tapping, SRT and CRT (auditory, visual cues)	Siemers et al, 1996	Alternate tapping, auditory and visual reaction time MHD and other groups, p <0.05, PMGs and NGCs no difference.	The changes in PMGs were not grossly evident, however since CAG repeats and test performance for movement time had a correlation, subtle motor changes are present in PMGs who have inherited the allele.
21.	PMG and controls	Tapping with four fingers in Simple and complex sequences based on the metronome with imaging	Kloppel et al, 2009	Error rates were between 2 – 7 % in PMGs, and 0.5 to 4 % in controls, and increased caudal SMA activity in PMGs.	Motor decline is subtle, and also a preclinical shift from premotor to parietal regions to compensate in executive and cognitive motor areas.
22.	PMG	Externally paced tapping task (auditory cue) followed by internally paced	Hinton, Paulsen, et al 2007	IRI did not correlate with predictability of onset, SD of IRI showed a correlation	Motor timing did not appear to change closer to onset, however motor variability decreased linearly with years from onset.
23.	MG vs controls (Sample size 4 MG)	Tapping frequency, tapping speed, Reaction time, and reduced striatal glucose	Garnett et al, 1984	RT was >400ms(prolonged by 100 ms) in the MG group, and 250 – 300 ms in controls	Reaction time was prolonged all subjects in MG of HD

		cosumption			
24.	MG vs healthy controls	Response inhibition tasks in go and No/go trails (Choice reaction time/CRT)	Beste et al, 2007, 2008	Reaction time, p <0.004 Go trials, HD vs controls, p< 0.168, No go trials – Reaction time, p <0.004, Number of false alarms in no go trials, p < 0.01	Though reaction times were not prolonged, response inhibition was affected in the MG group. In the no go trials, the number of false alarms raised and reaction time were increased.
25.	MG vs healthy controls (8 HD)	Speeded tapping, Alternate tapping, pronation, supination of the forefinger to tap the target	Antoniades et al, 2012	Reciprocal of reaction time or IRI in single speeded tapping, p <0.036, R values are significant for supinating, pronating and single speeded tapping	In smaller sample sizes, IRI is skewed. Its reciprocal shows significant difference MG and controls in single speeded tapping, as it is impaired in MG of HD.
26.	14 PD, 9 HD and 7 dystonia patients	Sequential arm movements	Agostino et al, 1992	Clockwise, p <0.005, anti clockwise p <0.001	Though all sequences were performed, there was a marked delay in time taken to perform both types of sequential arm movements in MG of HD.

5.4 Common finger tapping tests with various devices, as evidenced by the table are:

1. Fast tapping with single finger.

   Tapping at the fastest speed with a single finger on a specified target.

2. Fast alternate target tapping with single finger

   Tapping at the fastest speed with a single finger, on two separate targets alternately.

3. Self paced tapping with single finger

   Tapping at their speed with a single finger.

4. Self paced tapping with two or more fingers.

   Tapping at their own speed with a single finger, on two separate targets alternately.

5. Finger Tapping based on auditory cues.

   Tapping to an external auditory cue in the form of a beep or a set of beeps.

6. Finger Tapping based on visual cues.

   Tapping to a visual cue in the form of the appearance or disappearance of a stimulus.

7. Finger tapping based on a metronome

   Tapping to a set frequency of the metronome.

8. Simple reaction time – Response to a stimulus in the form of finger a tap.

9. Choice/Complex reaction time – Response to a stimulus, in the form of finger tapping, which also includes the process of decision making of the type of tapping response.

10. Rapid supination and pronation of the finger at the knuckles (proximal inter-phalangeal joint).

11. Rapid pronation and supination of the hand on the target.

12. Tapping of two or more fingers together on a specified target.

Other measures such as velocity and force (in the form of acceleration) of the fingers while tapping may be obtained through tapping tests.

While it would not be within the scope of this study to specify the procedure of all the above tests, a tabulated version (above) of these studies gives an overview

of the type of results obtained. Some tasks have been more successful in obtaining useful information pertaining to the motor decline in these neurodegenerative disorders. Based on this literature review, we chose 5 tasks, which show promise in obtaining information to identify and monitor PD and HD. The measures that the ideal finger-tapping task can identify are described below.

5.5 Motor performance assesses dyskinesia, dysrhythmicity and force

Studying dyskinesia (bradykinesia), dysrhythmicity and force can assess motor performance in a movement disorder. An objective measure of these parameters can be obtained by appropriate tapping tasks, which specifically have the ability to measure these parameters.

Bradykinesia

Bradykinesia is one of the cardinal signs in PD, which is associated with disturbances in the execution of normal motor rhythm (Ali et al, 2006). It is understood that one of the reasons that there is a considerable difficulty in performing movements at a constant rhythm is that the internal clock which helps in the execution of normal rhythm is disturbed (Pastor et al, 1992,O'Boyle, 1996, P. Severine et al, 2005). Tapping tests, which measure speed of movements, can objectively measure bradykinesia. Studies involving repetitive movements such as speeded, paced or self-paced finger tapping have shown that PD patients tapped at a slower rate than controls (Refer Table 5.3, 5.4), and some PD groups (tremor predominant) performed better than others (Yahalom et al, 2004). Similar studies on finger tapping alone, be it speeded, alternate finger or pronation, supination have shown consistent findings that controls performed better at tapping tasks than PD patients in terms of speed, and consistent rhythm.

Dysrhythmicity

Dysrhythmicity as explained above is due to disturbances in the internal clock. This is important with reference to basal ganglia disorders, because internal timing processes in both time perception and motor timing processes are mediated by the basal ganglia (Chamberlain et al, 2006,Naomi et al, 2010). Therefore, basal ganglia disorders can be studied by objectively measuring dysrhythmicity. Dysrhythmicity can be assessed by means of simple finger tapping tasks, which aim to measure the ability to maintain constancy of rhythmic actions, and thereby may provide a measure of the patient's motor decline. Tapping rates, and inter-tap intervals are parameters in finger tapping tasks, which can provide an objective measure of dysrhythmicity and thereby reflect basal ganglia dysfunction.

Studies involving rhythmic movements and self-paced finger tapping have identified that controls performed better than PD groups, irrespective of the stage of the disease. However, patients with PD can improve their motor performance when they have external cueing, compared to self-initiated movements or internal cueing (Kirkwood et al, 1999, 2000a, 2000b). While PD patients performed better with cues or training, the motor performance in HD does not significantly improve with cueing.

Observing finger-tapping patterns, aside from tapping speed alone can provide an insight into the manifestation of the motor decline. PD patients tend to tap too rapidly when instructed to tap at slower frequencies (1-3Hz), and too slowly when instructed to tap at faster frequencies (5Hz)(Klein et al, 2005). Nakamura described this hastening as a phenomenon among PD patients, as they tap at faster frequencies/rates than instructed (Nakamura et al, 1978). Furthermore, amplitude, rhythm and velocity of finger tap movements differ according to the patient's motor performance and symptoms, which is depictive of the stage of the disease (Yokoe et al, 2009a, 2009b).

Force/ Amplitude

Motor performance can also be measured by the force/amplitude of the tap. Patients with bradykinesia are expected to have a lower tapping force by virtue of time taken to perform movement and the force of impact, which is measured. Among several studies which showed a difference in tapping force in movement disorders, a difference in peak tapping forces were shown to vary among different HD groups (Bechtel et al, 2010, Tabrizi et al, 2009).

Although tapping in HD patients has been reported for a shorter time, there have been interesting results. Differences in tapping rates in finger tapping have been identified between HD groups, MG, PMG and non-gene carrier controls, however tapping measures such as ITI and variability have not been as thoroughly investigated. Inter-tap-variability (as an outcome of dysrhythmicity and dyskinesia) has been a sensitive motor sign in PMG gene carriers (Langbehn and Paulsen, 2007). Inter-tap-variability/latency was shown to be significantly higher between PMG and MG in HD (Antoniades, 2010, Kirkwood et al, 2009). The PREDICT – HD study revealed changes in hand tapping in the form of inter-tap variability detected one to two decades before the patient becomes manifest which shows promise in the ability of finger tapping to become a biomarker.

Though undertaken in separate studies, analyzing all aspects of motor performance in the form of tapping rate, inter-tap interval (IRI), IRI variability, force, speed of pronation and supination would be more useful clinically. The parameters, which can be gleaned from them, are many. However, the parameters, from one or many finger tapping tasks which can show a valid difference unaffected by other variables, need to be identified and standardized, thus revealing a hand/finger tapping biomarker to identify PD or HD.

5.6 Voluntary movement - Planning, Reaction Time

Voluntary Movement

Voluntary movement maybe described as movement based on volition. This action or movement is purposeful, and can be generated internally differing from the mechanism of involuntary movement and reflexes (Kandel, 2012: *Principles of Neural Science*).

Volitional movement is dependent on intact working of the basal ganglia (Fig 1.2, 1.3 Motor loop). Voluntary movement requires planning and execution mediated by the basal ganglia. By analyzing the break up of voluntary action, we can study the extent of impairment in basal ganglia disorders, even though compensatory changes may take place. Therefore, we are interested in reaction time movement tasks in this context, as they are based on the ability to plan and execute the action, which would serve as a reflection of the working of the basal ganglia (Jahanshi et al, 1992).

Reaction time tasks

Reaction time is the time taken to respond to a stimulus. There are different types of reaction time tasks, simple, choice -1, and choice -2. Simple reaction time tasks involve a stimulus, to which the individual needs to respond in the form of moving a finger, tapping or looking at/away from the stimulus. Choice reaction time tasks involve making a decision based on prior information received or training followed by which, the action stipulated needs to be executed. The choice reaction time includes an instruction, usually in the form of an auditory of visual cue. Hence the term cued task.

Fig 5.1 Simple reaction time

Simple reaction time test

Stimulus Presentation Reaction (Clicking button)

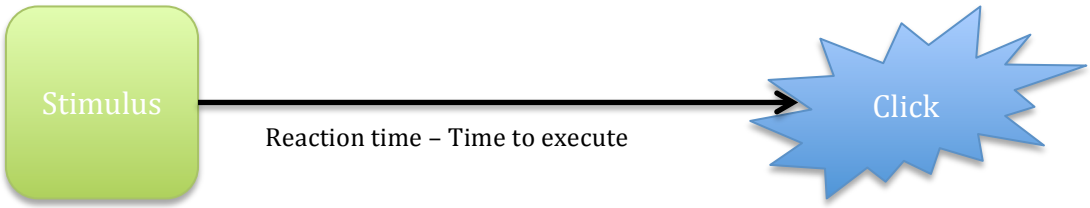
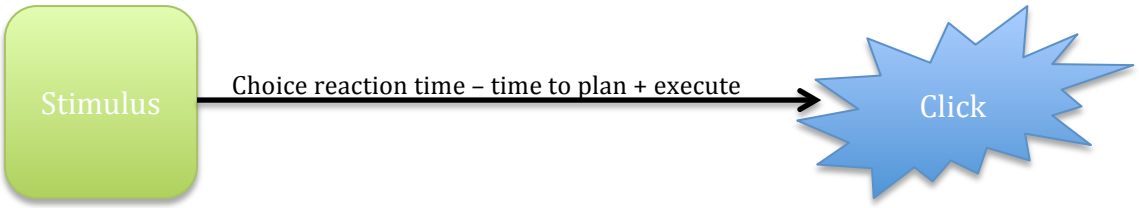
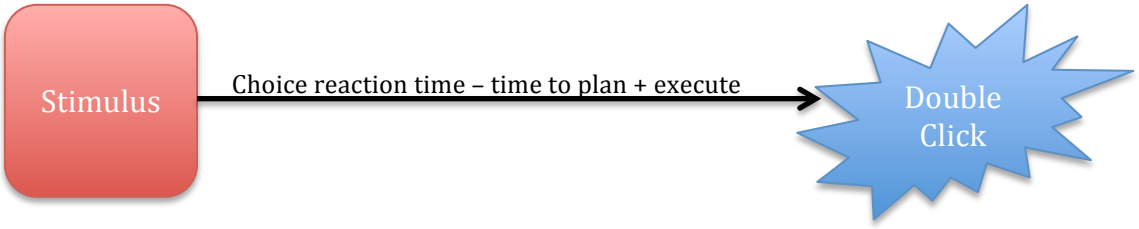


Fig 5.2 Choice reaction time

Choice Reaction time test

Stimulus Presentation Choice reaction (Green stimulus- click button)





Reaction time tasks in PD and HD

Reaction time is expected to be impaired in patients of basal ganglia disorders due to impairment in voluntary movements. Patients with Parkinson's disease are known to experience difficulty with volitional, sequential and simultaneous movements (Benecke et al, 1986, 1987, Catalan, 1999), although external cues may help improve performance (Georgiou et al, 1994, Martin et al, 1994). Other studies show that simple reaction time is longer in PD patients versus controls (Montgomery & Nuessen, 1990, Viallet et al, 1987, Jahanshi et al, 1992). Cued and uncued choice reaction time was also slower in PD subjects (Jahanshi et al, 1993). Different kinds of movement and reaction time tasks have been studied over the past two decades, with a focus on simple reaction time, which help to analyze the functioning of the basal ganglia. Impairment of the basal ganglia working can also be picked up by saccadic tasks of varying complexity (Lueck et al, 1990,Brian et al, 1999,) in a similar manner to tapping reaction time tasks.

Examples of tests in voluntary movement include movement (of the finger) between two points on the testing platform also known as alternate target tapping task, reaction time tests, or following a sequence as in UHDRS.

Similar to the tasks used in PD, tests which study movement between points and finger dexterity in manifest HD patients show significant deterioration over time (Paulsen et al, 2008, Saft et al, 2006, Ruiz et al, 2002, Antoniades 2010). However, simple reaction time with auditory and visual cues did not show any significant difference in HD patients (Kirkwood et al, 2000), although in the same study the movement time (time taken to move between points, with and without choice) was found to be significantly slower in HD patients. PET studies involving alternate finger tapping have been shown to be an objective measure of clinical severity of PD (Pal et al, 2001).

Studies of finger tapping in PD or HD so far have tested for specific disabilities like dysrhythmia, incoordination, and an inability to perform sequential tasks in different populations. However, only few longitudinal studies have been able to follow tapping abilities in HD patients over time (Langbehn, 2007, Antoniades, 2012, Andrich et al, 2007, TRACK -HD).

It would be ideal to study tapping disabilities in HD or PD, through a battery of finger tapping tasks, and to follow the group over time. Systematic studies testing finger tapping in risk groups of HD, such as pre-symptomatic gene carriers (PMG) before the onset of disease and after, as well as comparing them with the MG group have been performed in the TRACK and PREDICT HD studies. These have significant results in some parameters of tapping, although not in the reaction time in tapping tasks.

As evidenced by tables (Table 5.1 and 5.2) research on finger or hand tapping tasks in PD though many, have been mostly cross sectional. The results have been positive for externally cued tapping and alternate tapping, but the other results are mixed. However, hand or finger tapping tasks in HD have shown more consistency, albeit that they have been mainly about finger tapping, which is self-paced. More work is necessary in this area, to develop the type of tapping as an objective and standardized measure.

Clinical scoring like UPDRS/UHDRS is widely used to assess PD and HD even though they have inter-rater variability. It would be interesting if we can develop tapping tasks which correlate with some aspects of the scale, and therefore reduce inter- rater variability if they are used along with the UHDRS/UPDRS.

On the basis of this information, we have developed a set of finger tapping tasks, which test

1. Inter-tap interval (motor performance and ability to perform sequential movements).
2. Force/ Amplitude (motor performance).
3. Accuracy and precision (incoordination).
4. Ability to keep rhythm in self paced tapping tasks (dysrhythmicity).

Chapter 6

Aims & Objectives

6.1 Aims

1. Determine and compare changes in motor function and reaction time using finger tapping in individuals with manifest Huntington's disease.

2. Determine and compare changes in motor function and reaction time using finger tapping in individuals with Parkinson's disease.

6.2 Objectives

1. Develop an easy to perform novel finger tapping tool using an Android Tablet PC in the form of an Android application, by developing and identifying simple finger tapping tasks. These tasks will be based on motor and cognitive function, which can at the end of testing give a measure of the disease presence/absence as well as its clinical severity by providing sensitive and quantitative motor phenotype measures. The finger tapping tasks need to include speeded, externally and internally paced tasks, and tapping tasks based on simple and choice reaction time and complex reaction time.

2. Identify whether finger tapping can be used as a practical biomarker in movement disorders such as PD and HD by defining the relationship between finger tapping parameters and disease presence.

3. Identify if finger tapping through this android application can be used in a clinical setting as a practical tool to distinguish categorically between manifest HD, PD patients and controls.

4. Identify finger-tapping patterns in groups of different ages, and obtain baseline values for these parameters using this android application.

5. Identify tapping parameters worth extracting from commonly performed tapping and reaction time tasks.

6.3 Hypotheses:

1. Differences in speeded, metronome based tasks and reaction time based hand tapping tasks are detectable among different age groups.

2. Deficits in speeded, metronome based tasks and reaction time based hand tapping tasks are detectable in different early and late manifest groups of HD.

3. Deficits in speeded, metronome based tasks and reaction time based hand tapping tasks are detectable in PD.

Chapter 7

Experiment: Materials and methods

7.1 Participants:

7.1.1 Normal subjects:

45 normal subjects of different age groups were recruited from the John Radcliffe Hospital, Oxford. The participants had no significant medical disorder, which could affect their eyesight/hand tapping such as arthritis or alcohol dependency. A history of familial movement disorders was ruled out as well as any current neurological or psychiatric symptoms. Minor/major medical disorders, if any, were documented.

This group was subdivided into 3 groups of controls consisting of:

20 – 30 year olds

35 – 45 year olds

65 – 80 year olds

Group	Number	Mean Age
20 -30	15	24.6
35 - 45	14	39.7
65 - 80	16	74.5

Table 7.1: Grouping of controls into three age groups. 35-45 was originally chosen to match the age group of the HD subjects, 65-80 for PD and 20 – 30 to compare tapping patterns with younger populations.

7.1.2 Parkinson's disease subjects:

Participants were recruited from the movement disorders clinic at the John Radcliffe Hospital, Oxford.

Patients with PD were included in the study if they were older than 65 years, had been diagnosed with PD and had responded well to dopaminergic supplements. The diagnosis was confirmed by history and clinical examination by a movement disorders specialist. Clinical severity was assessed by Unified Parkinson's disease rating scale (UPDRS) as well as the Hoehn and Yahr scale. Exclusion criteria were associated neurological/psychiatric illness or being non - responsive to dopaminergic medication.

Patients were tested in the 'ON' state, when both the physician and the patient agreed that the medication was having its maximal effect.

The exclusion criteria were significant cognitive deficits, dementia or atypical Parkinsonism. Other exclusion criteria included deafness, blindness or any joint disorders.

This part of the study sought to compare differences between PD patients and controls, and included 21 patients and 18 controls.

Group	Number	Mean Age
PD patients	21	75.9
Controls	18	76.3

Table 7.2 Age matched groups of PD patients and controls

7.1.3 Huntington's disease subjects

Participants were recruited from the genetic disorders clinic at the John Radcliffe Hospital, Oxford. Patients with HD were included in the study if they had been diagnosed with HD, confirmed through clinical history, clinical examination and genetically by a genetic disorders specialist. CAG repeats were noted. The exclusion criteria were significant cognitive deficits, dementia, chorea or associated concurrent neurological or psychiatric illness. Other exclusion criteria included deafness, blindness or any joint disorders.

Group	**Number**	**20-30s (2)**	**35-45 (9)**	**65-75 (6)**
HD patients	17	27	36.9	74.2
Controls	18	25	34.2	75.7

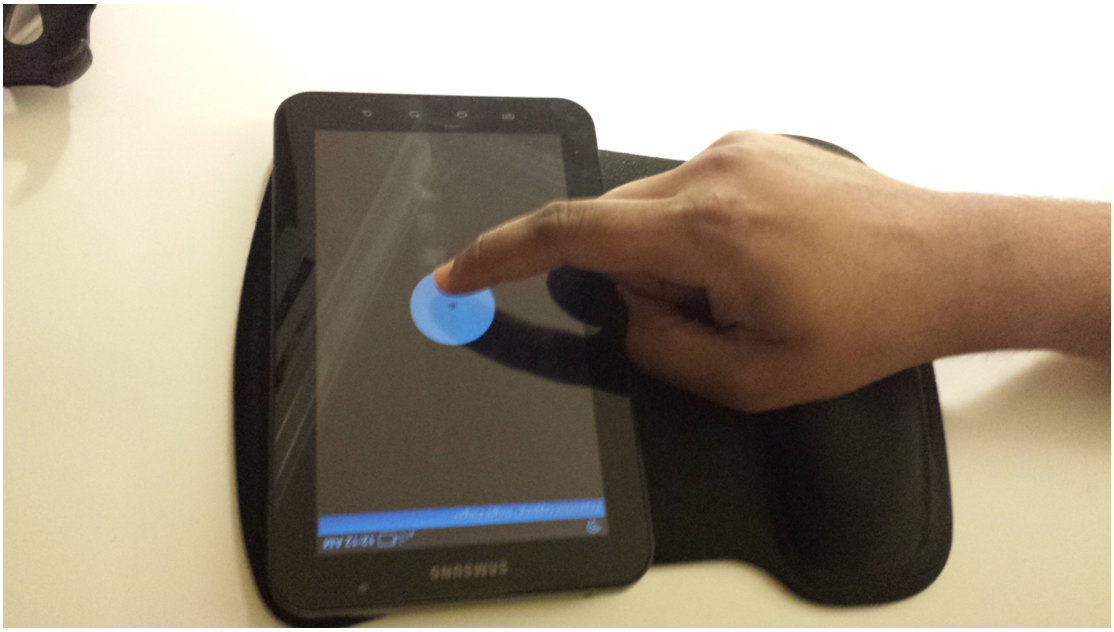
Table 7.3 Mean age and number of HD patients and age matched controls

7.2 Ethics

Local research ethics committee approval was granted for the experimental procedure. The approval is dated 02/09, REC No. 04/Q/0406/60. Informed consent was taken from each patient after explaining the study protocol, the confidentiality of the information, recorded along with assurance of no interference to the patient's treatment. The information regarding the study was explained using a standard protocol, in a language best understood by the patient.

7.3 Device

Fig 7.1: Device used for hand tapping: 7" Samsung Galaxy tablet, running on Android 2.2



The device is a Samsung Galaxy Tab 7.1' tablet of model number PT1000. Operating system: Android 2.2. The dimensions of the screen are 15.5 cm in length, 7.9 cm in width. The depth of the device is 1.1 cm. The results were stored in a database. Data retrieval was via a memory card or by connecting the tablet to a computer through which the test results were downloaded. Each patient was given a specific ID while taking consent, and this was used while storing data, to avoid identification of subject names. Each ID entered on the device created a separate folder and all test results pertaining to that ID were logged in, so that when that ID was entered, the particular patient's data alone was made available.

7.4 Software:

The tasks were programmed on Java 1.6. Android-based applications can be installed on devices operating with Android OS. Android API (Application Program Interface) 2.2 was used to develop the program. It is compatible with Android 2.2 and above.

7.5 Protocol

Each testing session lasted 50 minutes. The participant had to answer questions on a questionnaire (Appendix), after which the Edinburgh Handedness Inventory was performed to ascertain hand dominance.

Each participant was then seated in a chair in a comfortable position with their hands on the table. The chair height was adjusted, so that the table surface was at the level of the armrests. The tablet was placed on a special mat with a wrist pad on a stable surface.

The details of the tests were first explained to the patient. Instructions for each task, and actions to be performed were explained in a standard format for every subject. Refer to detailed protocol (Appendix).

The participants were allowed to perform a set of tasks to familiarize themselves with hand tapping on each task. To ensure an equal opportunity to learn, the same amount of time (20 seconds) and practice was given to each patient. Once each task was explained, the patient was allowed to practice for 20 seconds, and the same was repeated for the other tests. The testing commenced after the practice session with clear commands based on the protocol mentioned. The participants performed the practice session with both hands, dominant and non–dominant in random order, however for the actual test session, they performed first with the dominant hand, followed by the non-dominant hand. The order of the tapping tasks was randomized and the same sequence was used for all subjects.

7.6 Data Analysis

The data was downloaded onto a Macbook Pro. Each subject had a folder with data for all the tapping tasks, performed on dominant and non-dominant hands. Practice data was separated, and actual test files were tabulated on XL spreadsheets for each individual task. The program can provide a list of many variables, but the most relevant ones were chosen. These values were entered in a master XL sheet with data from controls. The final data was analyzed on SPSS 19.0 for the Mac OS.

Chapter 8

Experimental design

8.1 Type of Study

The study was divided into two parts:

1. A cross sectional study of 3 different age groups of individuals with no known health issues.

2. A case control study of age matched normal controls and subjects clinically determined to have PD and HD.

The subject or controls were seated comfortably on a chair, with hands on the table. The tablet was placed on a pad with padded support for the wrists. The subject was required to place their hand on the pad, with the wrist at its center such that the fingers were able to touch the surface of the tablet. Placing the wrist on wrist pad enforced restriction in movement, while ensuring the hand was at the level of the tablet (Refer Fig 7.1)

8.2 Tapping tasks

8.2.1 Self paced fast tapping – Single target.

Description: A white circular target measuring 3 cm in diameter is displayed on a black screen on the tablet PC. A central mark in the form of a red cross, to pinpoint the exact area to be tapped, is displayed within the white target.

The subject is instructed to tap on the target for 30 seconds, as fast as possible whilst maintaining consistency in rhythm, without moving the arm or wrist. This is a self-paced (fastest speed) task.

Time Duration: 30 seconds

Variables measured:

1. Tap Count: Number of taps on the 'target'.
2. Mean inter-tap interval (ITI): Time between each tap, in milliseconds.
3. Force: Force exerted by the finger for each tap on the target, in ms^2 (meter per $second^{2,}$ with reference to g - $9.8ms^{2)}$
4. Error count: Number of taps outside the target.

5. Displacement (d): The co-ordinates of each tap are measured. Displacement is calculated by using the co-ordinates of each tap, in relation to the co-ordinates (x,y) of the central tapping point(cross mark).

$$d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2}$$

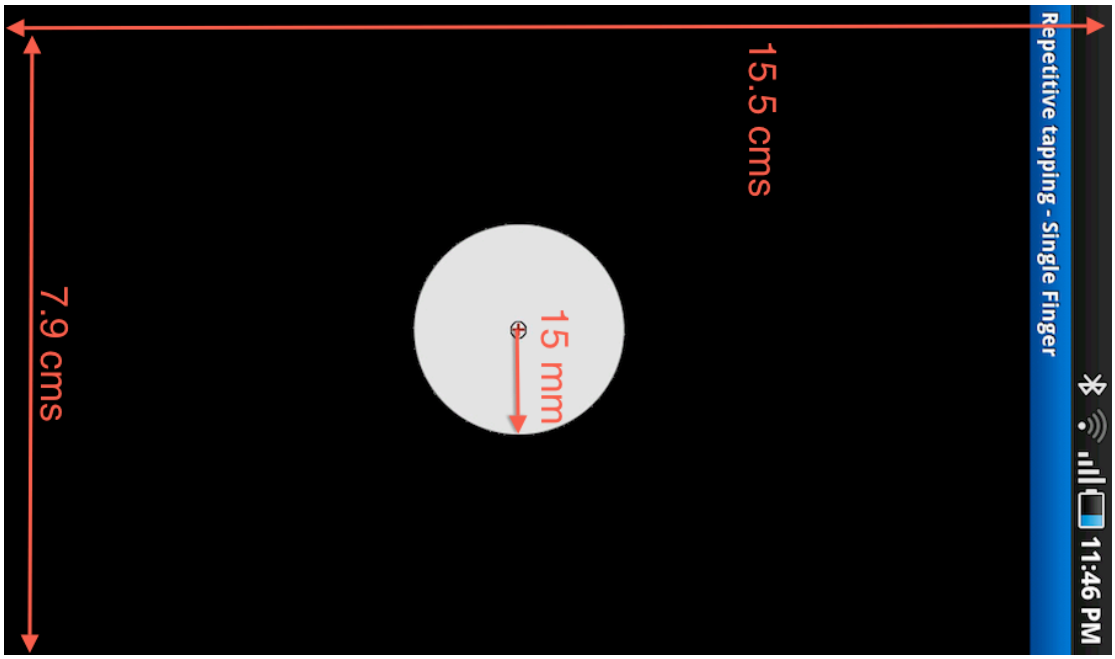


Fig 8.1 Tablet screen showing the first task and dimensions
The central target is 15 mm or 1.5 cm, while the length and width are 15.5 cm and 7.9 cm respectively.

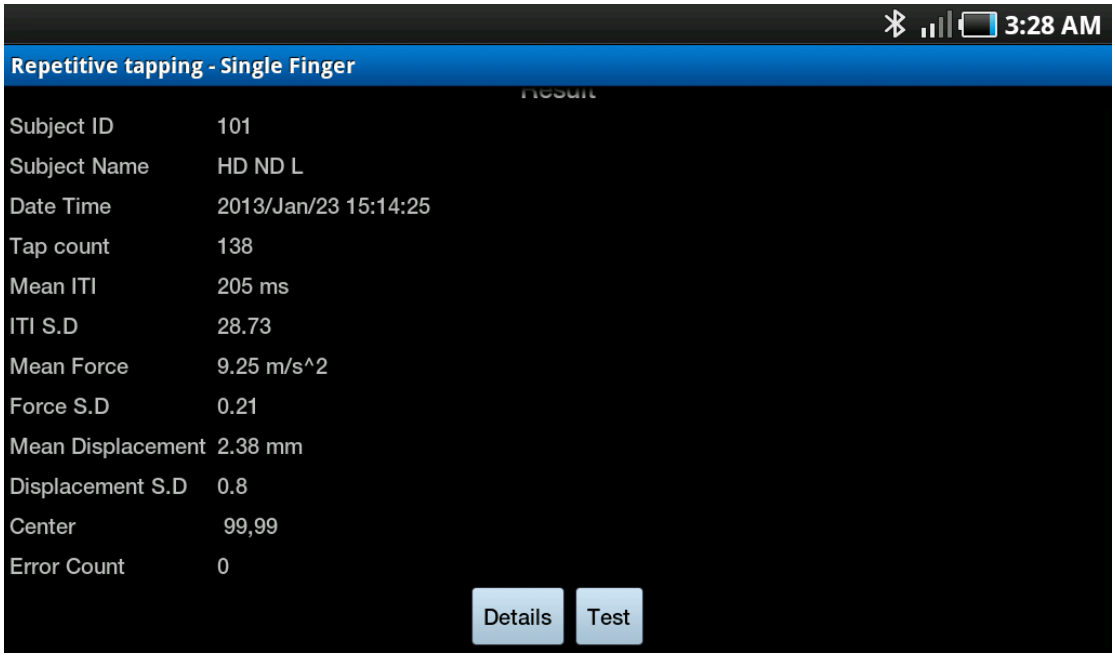
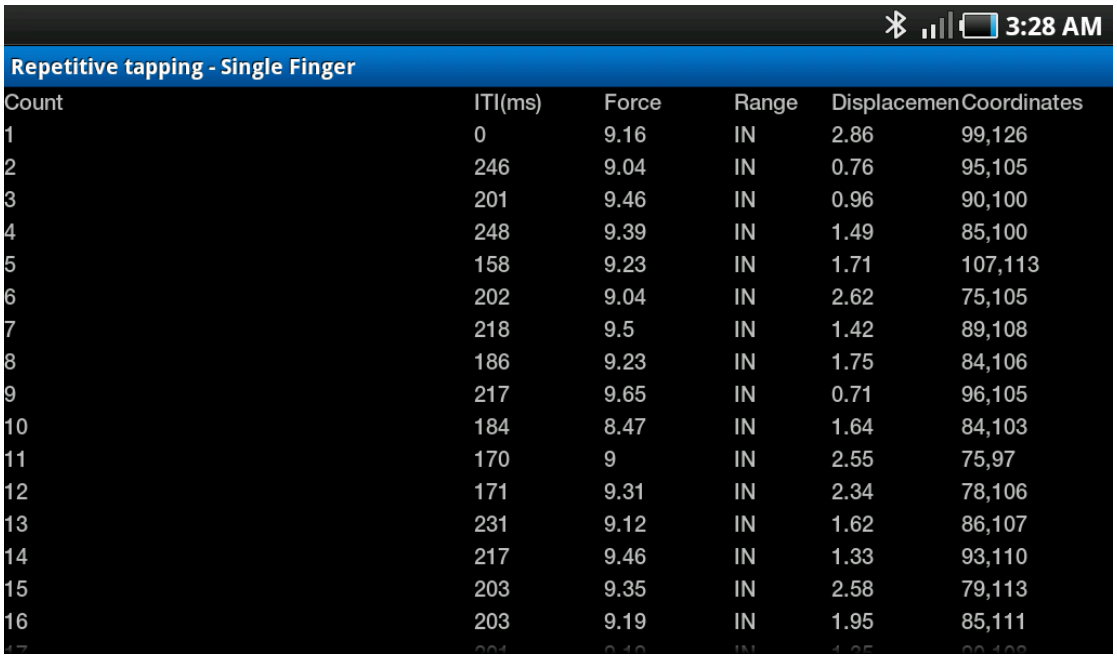


Fig 8.2: Test results on completion of self paced fast tapping task showing tap count, ITI, ITI Standard deviation, force, and error rate.



Count	ITI(ms)	Force	Range	Displacemen	Coordinates
1	0	9.16	IN	2.86	99,126
2	246	9.04	IN	0.76	95,105
3	201	9.46	IN	0.96	90,100
4	248	9.39	IN	1.49	85,100
5	158	9.23	IN	1.71	107,113
6	202	9.04	IN	2.62	75,105
7	218	9.5	IN	1.42	89,108
8	186	9.23	IN	1.75	84,106
9	217	9.65	IN	0.71	96,105
10	184	8.47	IN	1.64	84,103
11	170	9	IN	2.55	75,97
12	171	9.31	IN	2.34	78,106
13	231	9.12	IN	1.62	86,107
14	217	9.46	IN	1.33	93,110
15	203	9.35	IN	2.58	79,113
16	203	9.19	IN	1.95	85,111

Fig 8.3: Detailed results of every tap made during the self paced fast tapping task showing tap count, ITI, force value and co-ordinates.

8.2.2 Self paced fast tapping – Two targets

Description: Two white circular targets (R= Right, L= Left), each measuring 3 cm in diameter are displayed on a black screen. The distance between the centers of each circle is 9.2 cm. Just as in the first test; a mark in the form of a red cross denotes the exact point to be tapped.

The subject is instructed to tap alternatively on each target with the index finger, without moving the arm or wrist. Restriction in movement is enforced by placing the wrist on the wrist pad at the level of the tablet computer. Tapping is performed as fast as possible, whilst maintaining a consistent rhythm for 30 seconds. This task is self-paced and fast, and is also described as alternate tapping between two targets and involves the time for movement between them.

Time Duration: 30 seconds

Variables:

The variables are similar to those in Task 1

1.Tap Count R/L: Number of taps on the right or left targets(R/L) respectively.

2.ITI/ inter-tap interval: Time between each tap, in milliseconds.

3.Force R/L: Force exerted by the finger while tapping on the targets R/L respectively, in ms^2.

4.Error-Count R/L: Number of taps outside the targets R/L respectively.

5. Displacement (d)- R/L: The co-ordinates of each tap are measured. Displacement is calculated by using the co-ordinates (x,y) of each tap, in relation to the co-ordinates of the central tapping point on the targets R/L (cross mark).

$$d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2}$$

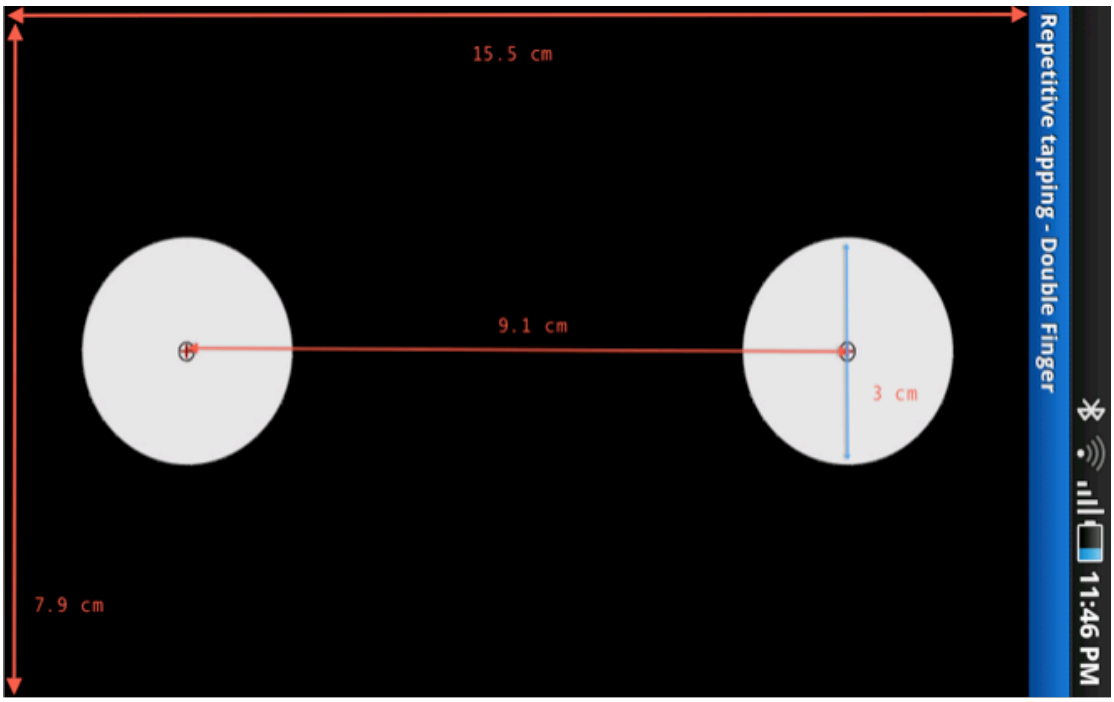


Fig 8.4: Tablet screen showing the second task and dimensions. The diameter of the target is 3 cm and the length and width are the same as in first task. The distance is 9.1 cm, comparable to other tapping devices such as the Ober. The maximum inter target distance possible in the device was used.

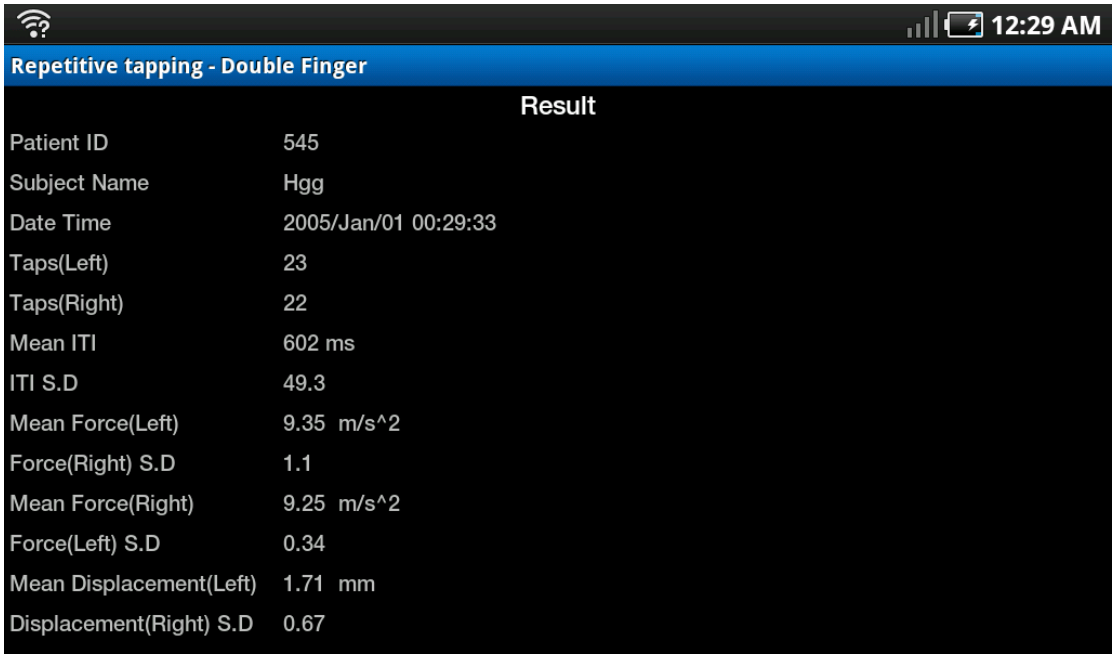
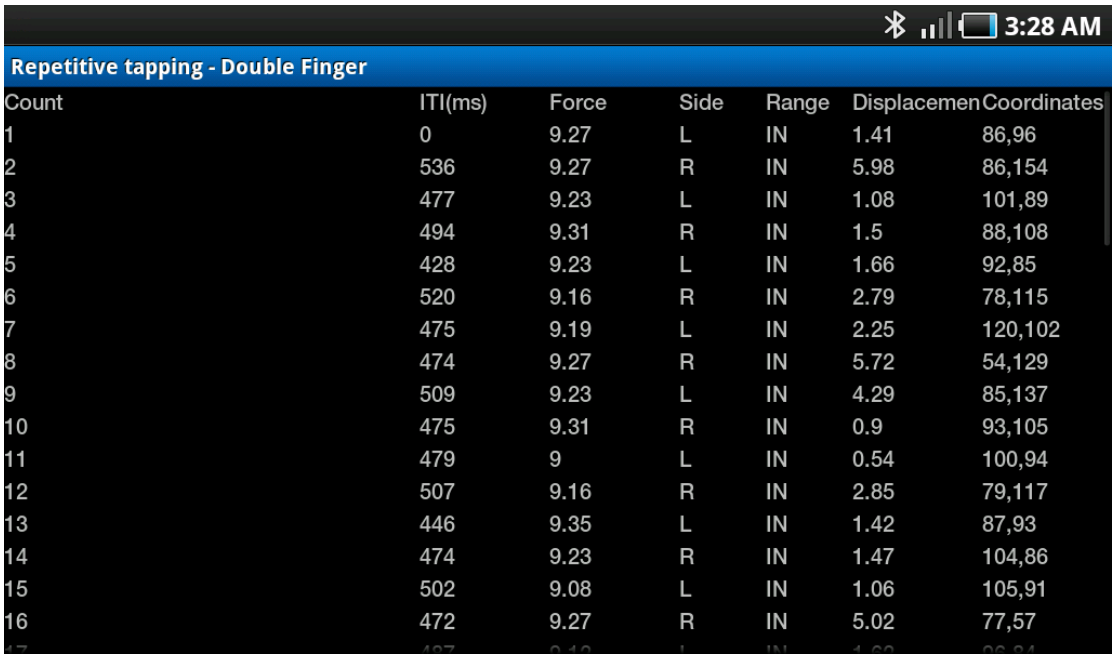


Fig 8. 5: Test results on completion of self paced fast tapping task with dual targets showing tap count, ITI, ITI Stand deviation, force, and error rate



Count	ITI(ms)	Force	Side	Range	Displacemen	Coordinates
1	0	9.27	L	IN	1.41	86,96
2	536	9.27	R	IN	5.98	86,154
3	477	9.23	L	IN	1.08	101,89
4	494	9.31	R	IN	1.5	88,108
5	428	9.23	L	IN	1.66	92,85
6	520	9.16	R	IN	2.79	78,115
7	475	9.19	L	IN	2.25	120,102
8	474	9.27	R	IN	5.72	54,129
9	509	9.23	L	IN	4.29	85,137
10	475	9.31	R	IN	0.9	93,105
11	479	9	L	IN	0.54	100,94
12	507	9.16	R	IN	2.85	79,117
13	446	9.35	L	IN	1.42	87,93
14	474	9.23	R	IN	1.47	104,86
15	502	9.08	L	IN	1.06	105,91
16	472	9.27	R	IN	5.02	77,57

Fig 8.6: Detailed results of every tap made during the self paced fast tapping task with dual target showing ITI, tap counts, force/ acceleration and co-ordinates on each target.

8.2.3 Tapping to auditory tones.

Description: The third task involves a set of five different frequencies of 1, 1.33, 2, 2.5 and 4 Hz. As described earlier, frequency is a measure of inter tap interval. Since frequency and wavelength are inversely proportional, the corresponding wavelength or number of times the tap is made are calculated, therefore at 1 Hz, an inter- tap- interval of 1000 milliseconds must be followed, 2 Hz – 500 ms, 1.33- 750 ms, 2.5 Hz – 400ms and 4 Hz – 250 ms.

A beep will play at the first frequency for 10 seconds, followed by a period of silence for 10 seconds, when no sound is played. The second frequency continues and so on until the fifth. The beep plays at any of these frequencies in random order except for the fastest 4 Hz and 2.5 Hz, which never play first to allow a minimum time for adaptation.

The test begins with the appearance of a central circular target measuring 3 cm in diameter, on the touchscreen. The participant would be required to tap according to the frequency or inter-rate interval at which the sound (first frequency) is played, after which there is a period of silence, when the subject is required to continue to tap with the same frequency, albeit without the sound. The frequency at which the subject tapped with and without the auditory cue is documented. The time when the tap is made, in relation to the time when the

beep occurred is also recorded. The rest of the test follows in the same pattern for the rest of the frequencies. At the end of the silence period of the fifth frequency the test comes to a stop, with a loud beep in tandem with the frequency. This is an example of external cueing, followed by the subject continuing to perform the voluntary movement with the same timing.

Variables:

1. 1 Hz /1000ms block: The frequency at which the subject tapped, when the sound played at 1Hz.
2. 1 Hz /1000ms Rest: The frequency at which the subject tapped, during the silent period following the 1 Hz block.
   Similarly block and rest frequencies of the other frequencies are generated for 1.33, 2, 2.5, 4 Hz block and rest periods.

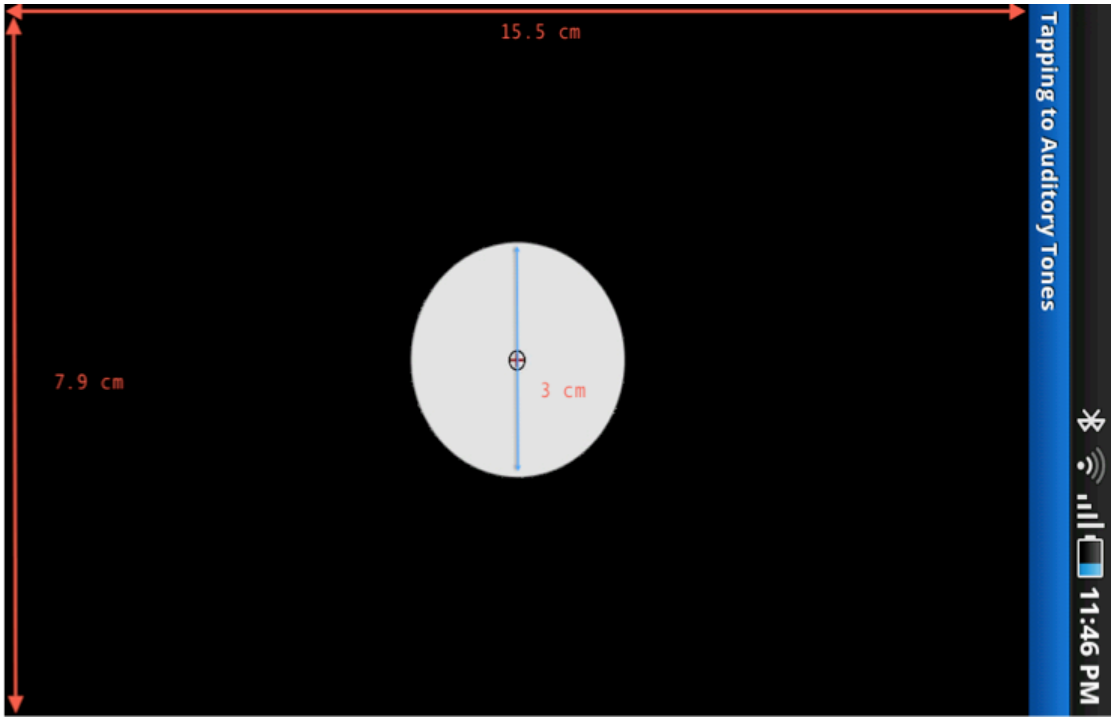


Fig 8.7: Tablet screen showing the third task. Dimensions and target remain the same as first task.

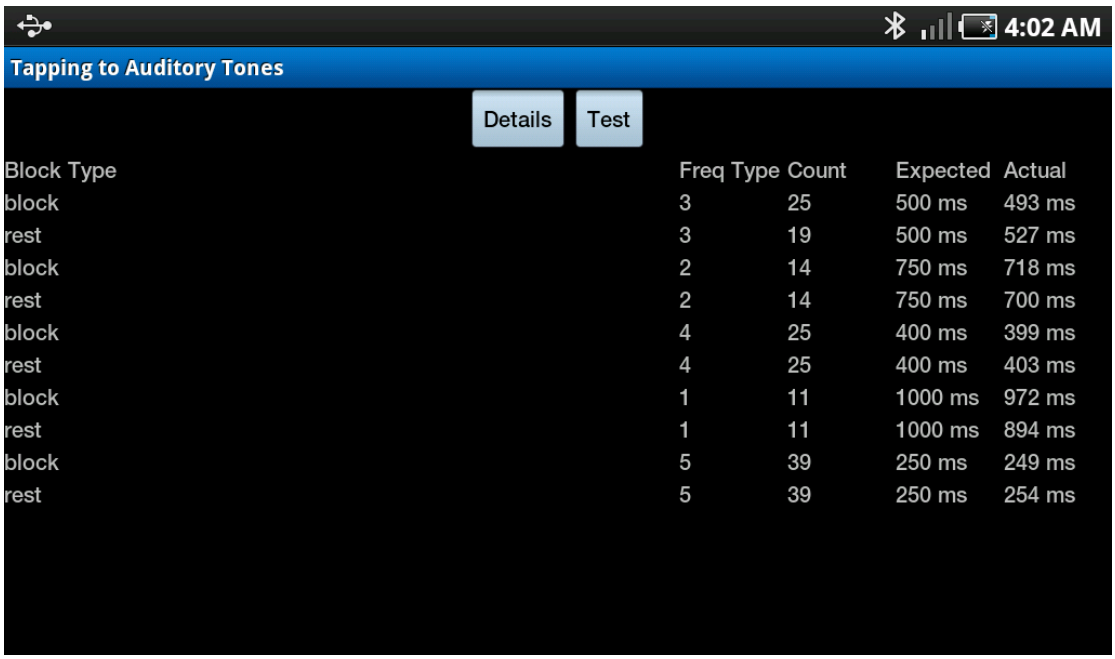


Fig 8.8: Test results on completion of the metronome task showing average tapping frequency of each frequency block with and without external cueing.

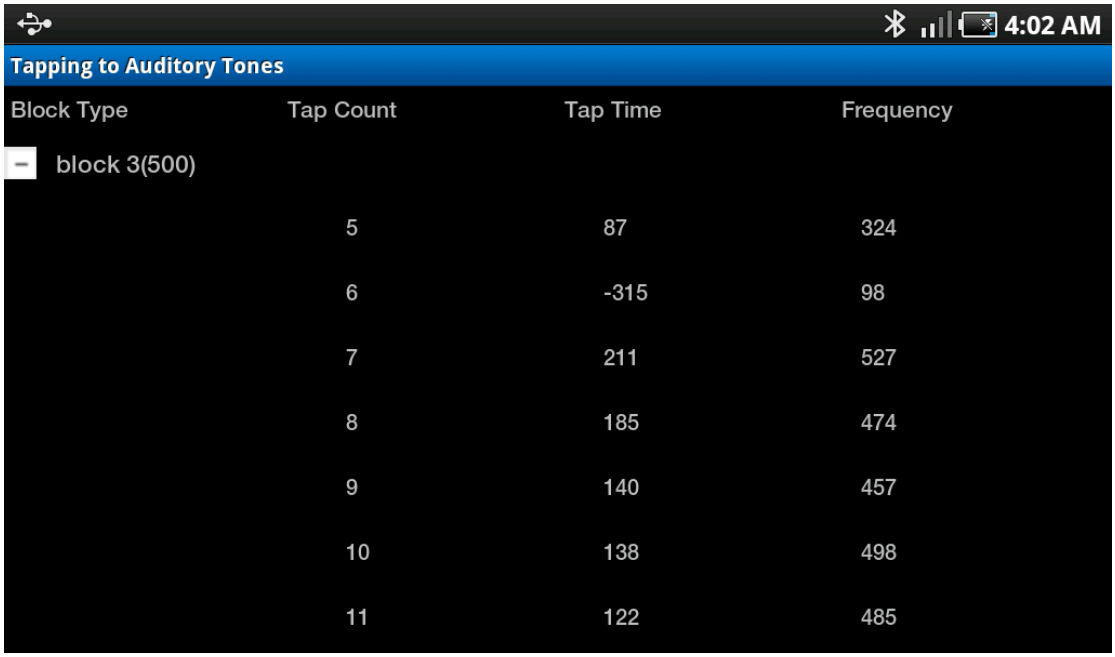


Fig 8.9: Detailed test results on completion of the metronome task showing individual frequency of every tap (ITI) for each frequency block.

8.2.4 Reaction time task (pro-tap)

Description: A white central square with sides of 2.5 cm, appears on the black screen. This is the fixation square. The subject is instructed to press and hold the central square. After a variable time period of 1300 +/- 500ms, another white square of the same size appears either to the right or left, at a distance of 3.05 cm from the edge of the central square. On the appearance of the target square, the subject is instructed to release the fixation square and tap on the target square immediately.

The target square will appear to the right or left of the fixation square, in a random order. There are 20 trials, 10 each to the right and left. The time for the appearance of the central fixation square is 500ms +/- 150ms. Since, this task is adapted from the saccadic task, the fixation square, where the index finger stays at all times, is present except when the stimulus is present.

Variables:

1. Reaction Time: Time taken to tap the target square from the time it appears on the screen.

2. Error Rate: Percentage of trials when the subject taps on the incorrect side.

   Error Rate = number of times taps were made on the incorrect side/ number of times the target square appeared on that side X100

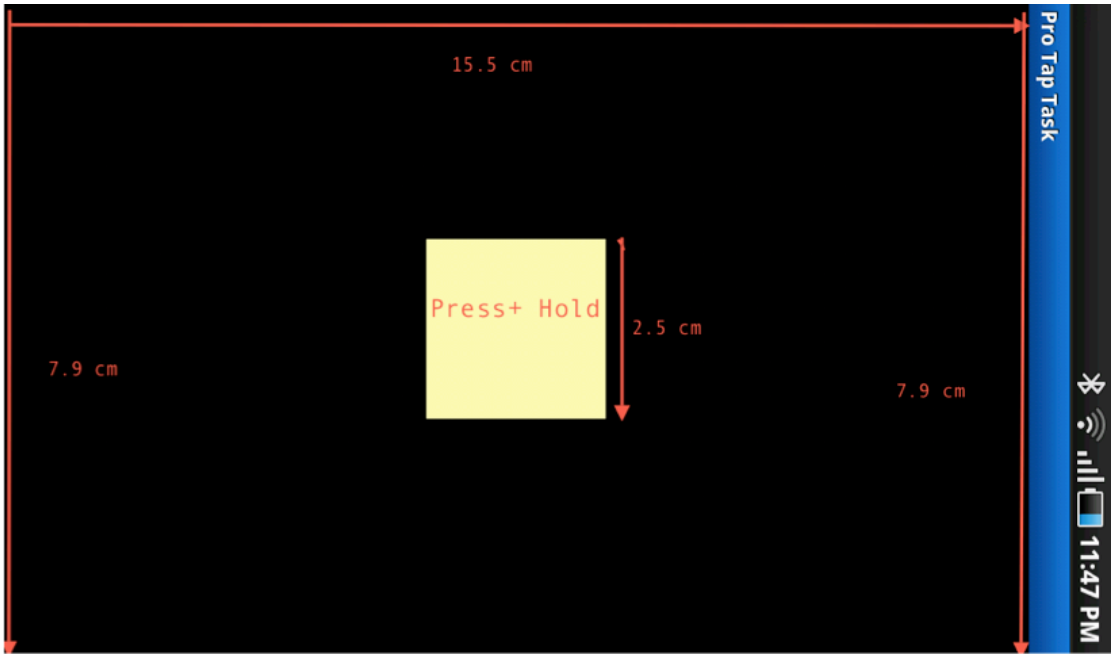


Fig 8.10: Tablet screen of the pro tap task. The dimensions of the test screen are identical to the other tests. The central target is a square of side 2.5 cm.

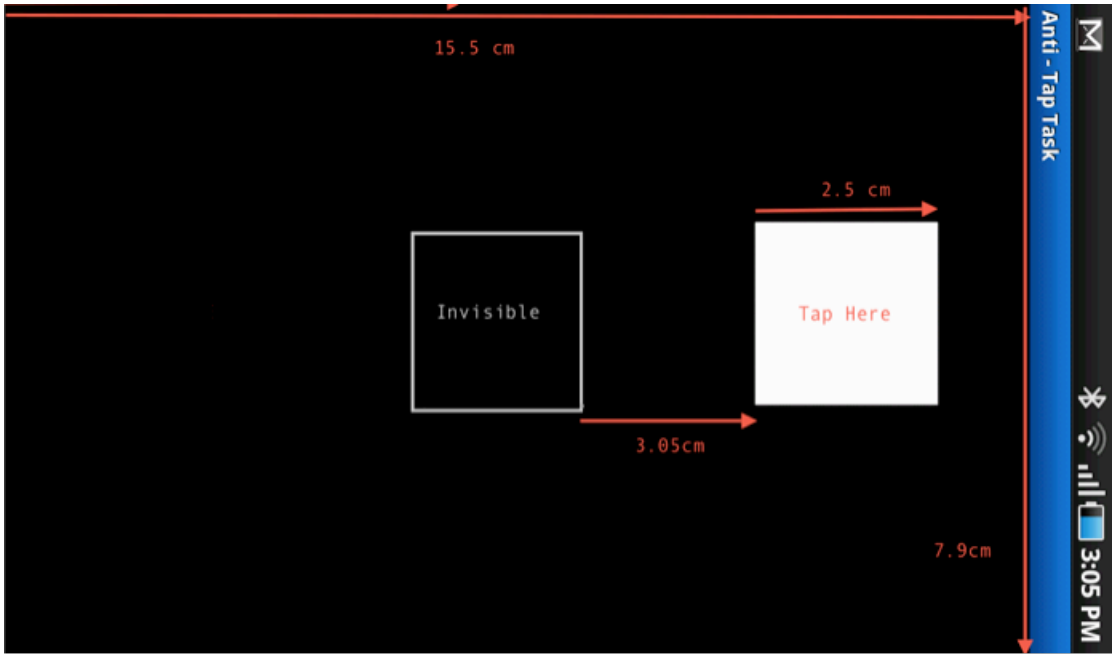


Fig 8.11: Tablet screen showing target movement in the pro-tap task. The target disappears from the center to appear at a distance of 3.05 cm at varying pre determined time intervals.

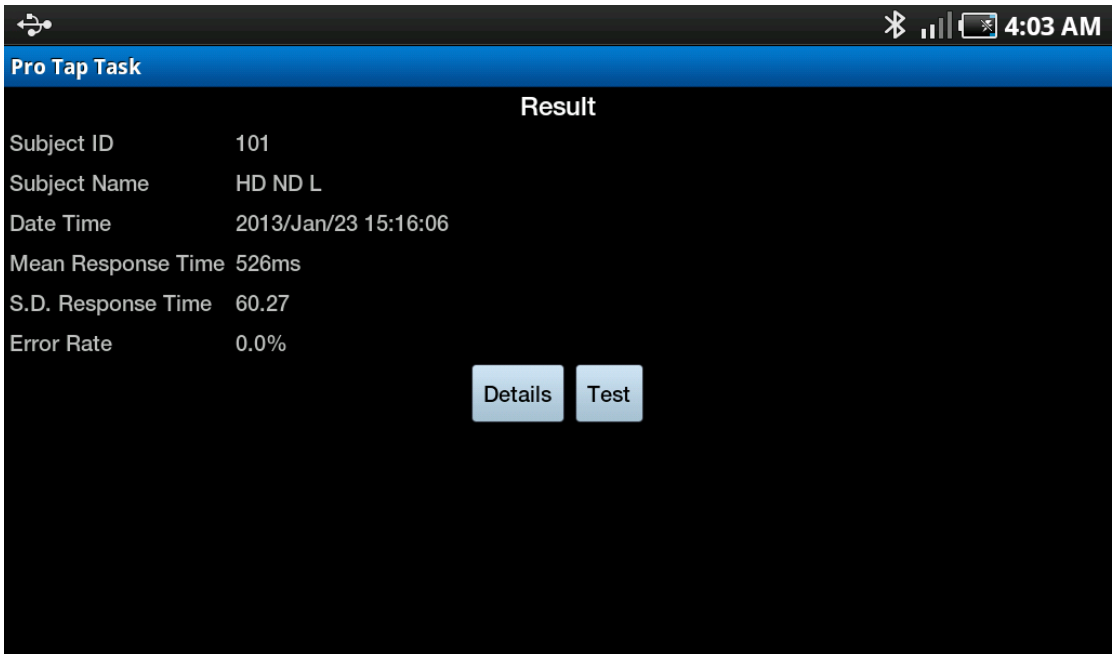


Fig 8. 12: Test results of the pro tap task showing mean reaction time, stand deviation and error rate.

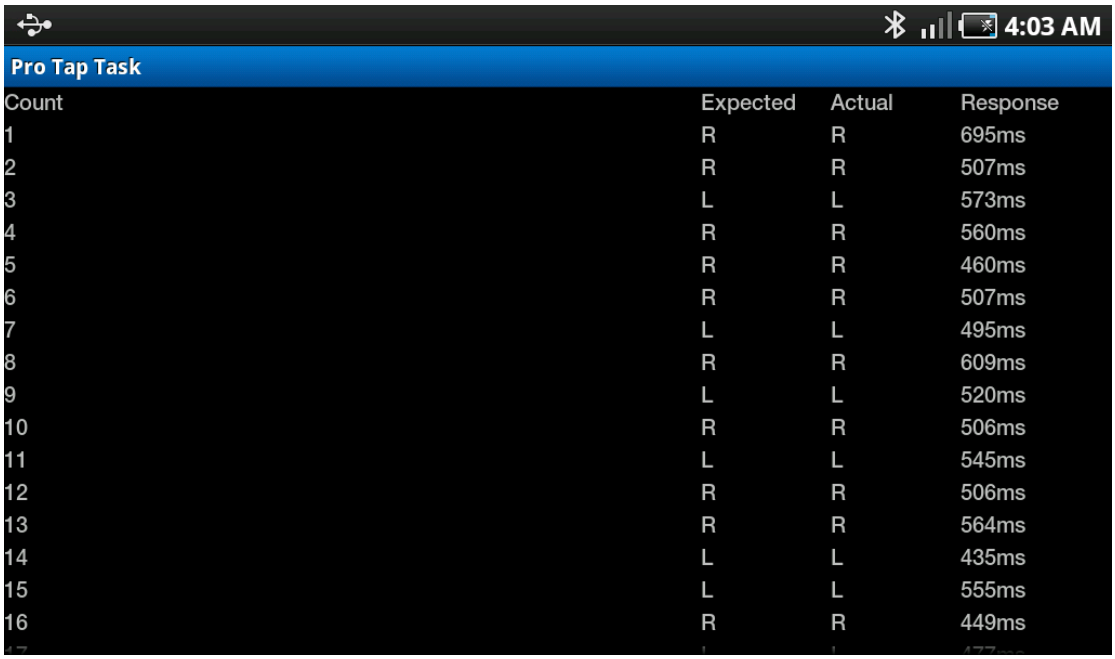


Fig 8.13: Detailed results of the pro tap task showing reaction time, and area tapped for each trial.

8.2.5 Choice reaction time (anti-tap) task

Description: The paradigm is identical as the simple reaction time task, except on appearance of the target square, the subject is instructed to release the fixation square and tap on the opposite side of the appearance of the target, i.e, black screen area. There are no landmarks to specify the region to be tapped.

The target square appears to the right or left of the fixation square, in a random order. 20 trials were undertaken, 10 each to the right and left. Time of the appearance of the central fixation square is 500 +/- 150ms.

The time taken to perform the voluntary action is recorded, along with the location of the tap.

Variables:

1. Reaction Time: Time taken to tap the target square on its appearance. Calculated as the time from when the target square appears to the time when the opposite part of the black screen is tapped.

2. Error-Rate: Percentage of wrong trials performed.

   Error-Rate = number of times taps were made on the target/ number of times the target square appeared on that side X100

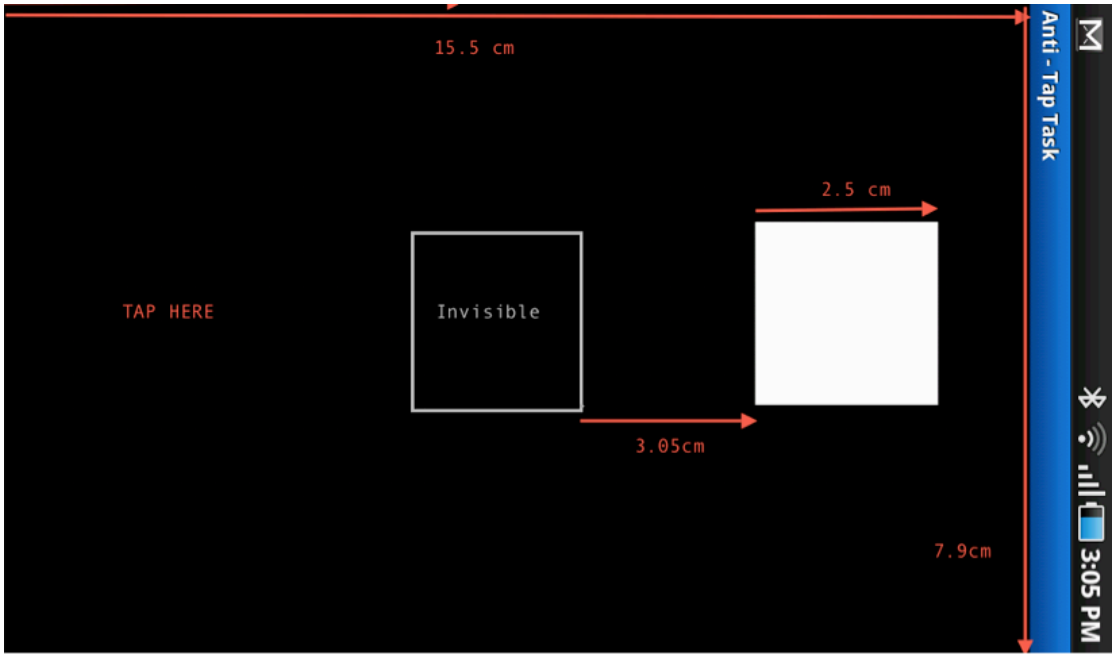


Fig 8.14: Tablet screen showing the anti-tap task. The dimensions of the test screen and target remain identical. The tapping area (in red) is shown on the opposite side of target appearance. Though invisible, the sensitive area, which identifies the tap, is identical in size to the target square and is located at the same distance from the central point.

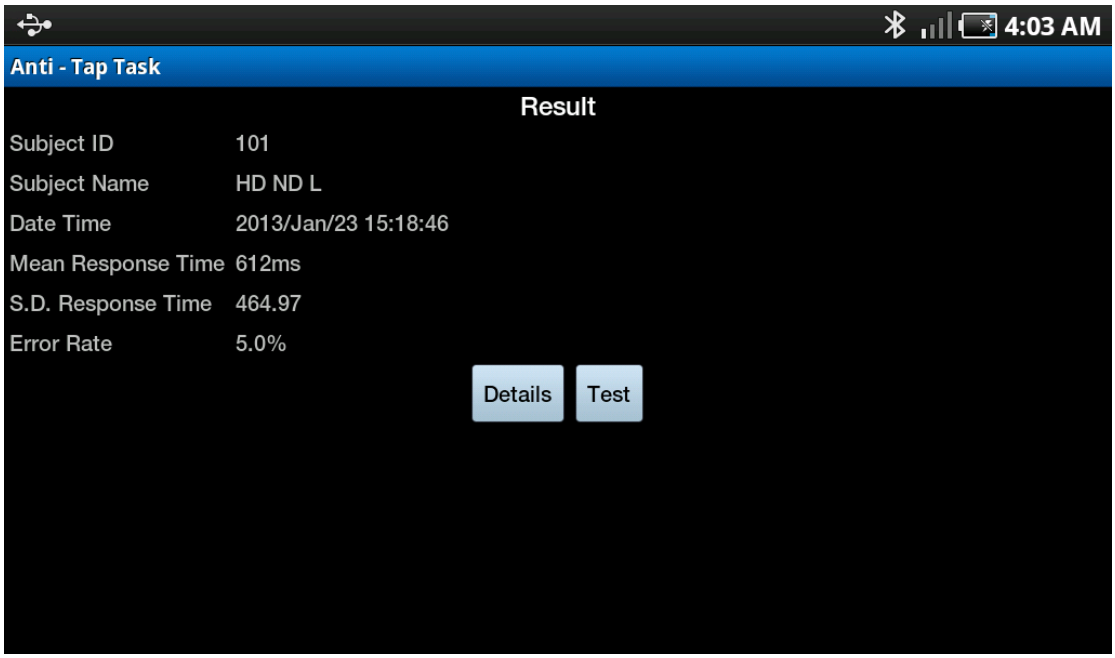


Fig 8.15: Test results of the choice reaction time task showing mean reaction time, standard deviation and error rate.

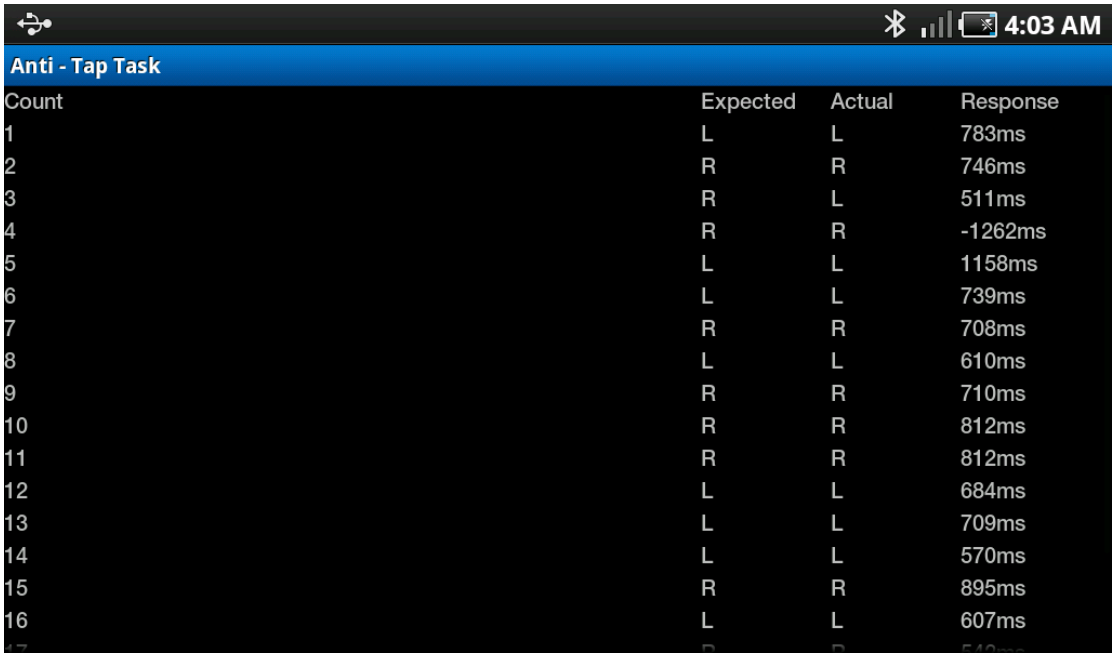


Fig 8.16 Detailed test results of the choice reaction time task , showing the reaction time, and tapping area of each trial

8.2.6 Conflict Task

Description: The paradigm is identical to the pro-tap task. However, when the target appears, a visual cue in the form of a red or green circle will appear above the location of the central fixation square which is extinguished when the peripheral target appears.

The visual cue provides the condition for tap or anti- tap. If there is a green circle above the fixation square, upon releasing the finger from the fixation square, the subject is instructed to tap on the target square (pro-tap). If there is a red circle above the fixation square, the opposite side (black screen area) of the target will have to be tapped (Anti-Tap). Since, this task is adapted from the saccadic task, the fixation square is present, where the index finger stays at all times except when the stimulus is not present.

The time taken to perform the voluntary action is recorded, along with the location of the reaction. The number of pro and anti taps performed, the time taken to react to that particular stimulus, is calculated. Errors for the go and no go, that is pro and anti tap trials are also recorded.

Variables:

1. Reaction Time: Time taken to tap the target square/opposite tapping area on its appearance. Calculated as time from when the target square appears to the time when the area is tapped.

2. Error-Rate: Percentage of wrong trials performed.

   Error-Rate A = Number of times taps were made on the incorrect side/ Number of times the target square appeared on that side X100

   Error-Rate B = Number of times taps were made on the correct side/ Number of times the target square appeared on that side X100

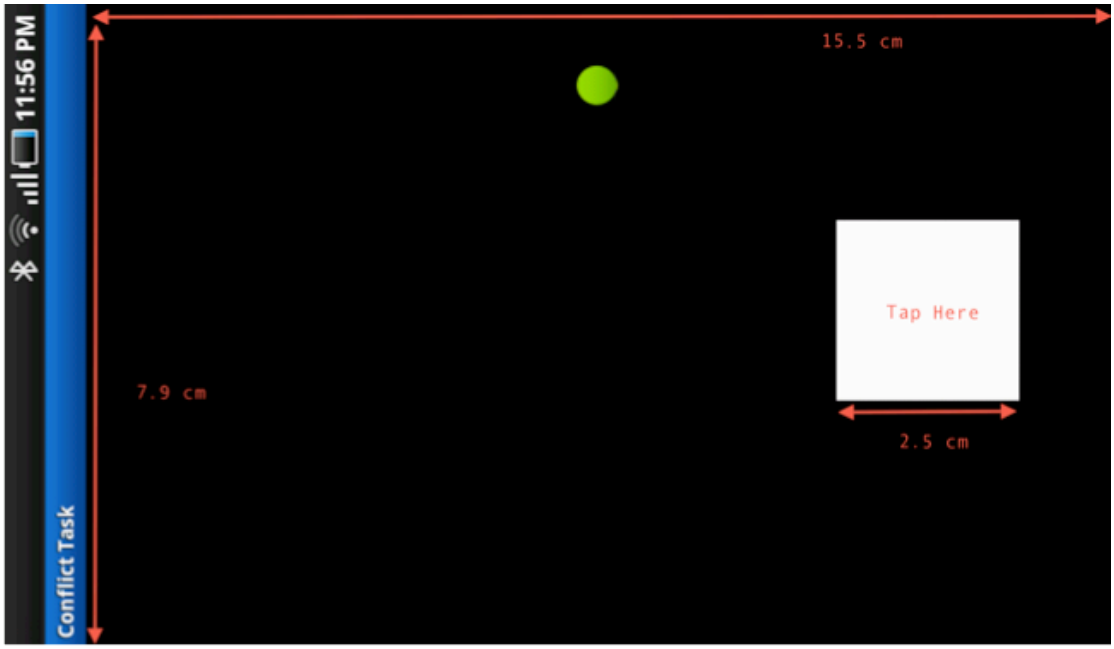


Fig 8.17: Tablet screen showing the conflict task. The test screen dimensions and target size remain the same, with the addition of a go or no go sign denoted by a red or green dot. The green dot shown above signals that a pro-tap must be made on the target.

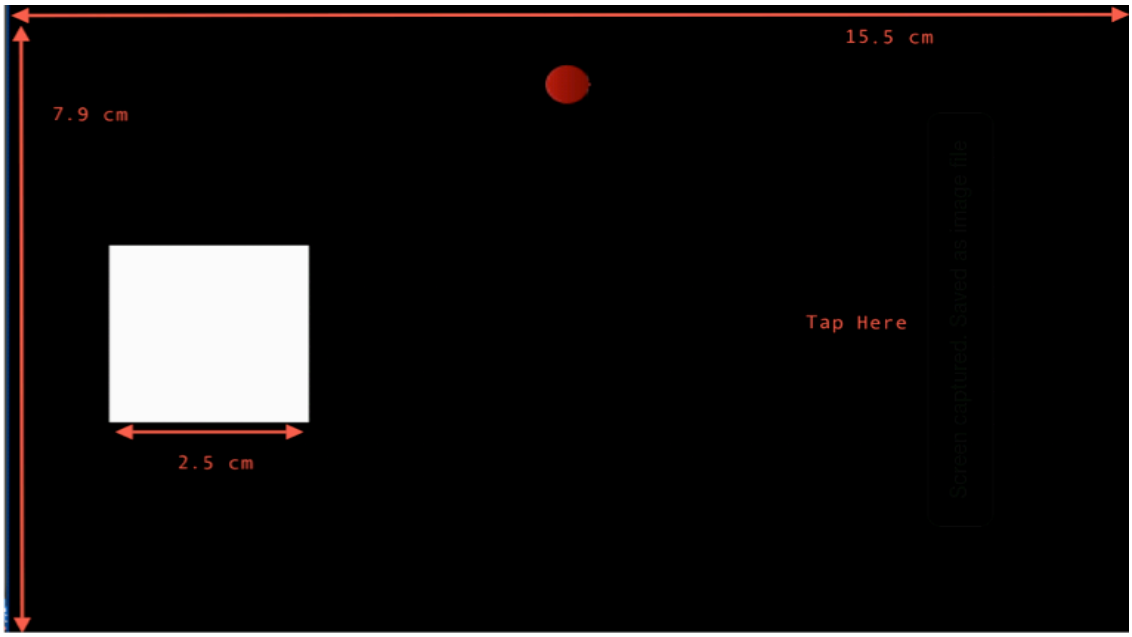


Fig 8.18: Tablet screen denoting the red dot signaling the cue to make an anti-tap (area opposite to the target appearance).

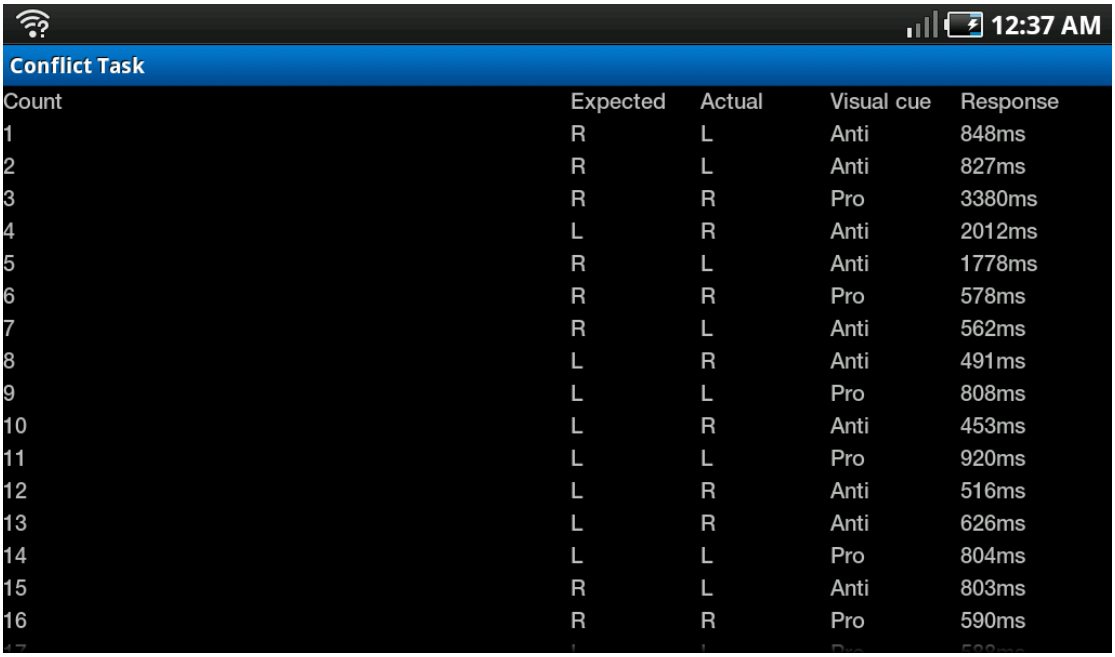


Fig 8.19: Test and detailed results of the conflict task showing mean reaction times, standard deviation and error rate.

8.3 Overview/Rationale of Experimental Tasks

Five important different finger-tapping tasks have been chosen for our study, on the basis of the studies in tapping and reaction time tasks (involving finger tapping).

8.3.1 Speeded or fast tapping - Single target

Speeded tapping involves a set period of time given to the patient, during which they are expected to tap as fast as possible on a chosen target. The target may be a force transducer, or a metal plate, which is a touch sensor ex: Ober (Antoniades et al, 2010). The number of times the finger touches the target during the time given is counted, and is called the tapping rate. The size and dimensions of the target are small enough to pick up an inability to tap accurately, and large enough to pick up small deviations from the center of the target.

The index finger is crucial for fine, motor tasks minimizing the potential impact of motor learning (Bechtel, 2010), and hence the most common method involves the use of the index finger. Some studies test the dominant and non-dominant hand. Some in the case of PD test the affected and unaffected side, and some use only the dominant side.

Speeded single finger tapping is able to test parameters such as:

1. Coordination (Tap Rate), obtained by counting the number of taps.
2. Rhythmicity (ITI) - The time between each tap, which would include the execution and movement time.
3. Accuracy (Displacement) – A measure of how deviant the tap was from the supposed target.

The presence of a single target, reduces wrist movement, and decreases the margin of error, due to reduced movement.

8.3.2 Speeded or fast tapping - Double targets

Speeded tapping with a double target involves the use of the index finger to tap on two adjacent targets. The distance between the two are specified, but are different on the devices used so far. The individual is required to tap between the two as fast as possible. The number of taps was counted in previous studies, along with the time between each tap (ITI).

Speeded tapping on double targets tests parameters similar to those with a single target. However, since this test involves movement between the two targets, steps must be taken to reduce extra movement, which can affect the ITI of the taps. This restriction has not been noted in other studies, as it is relatively difficult to achieve.

8.3.3 Metronome based tapping

As described earlier, metronome based tasks have been previously conducted in PD and HD. Some of them include tapping to an external cue (the metronome) for a period following which the cue is removed and the individual has to continue to tap at the same interval as tapped with the help of the external cue. Some studies involve tapping to a set frequency to which the individual is required to tap to, and the deviations in rhythm are measured. This task has had mixed results so far, as the variables are difficult to extract. A useful parameter could be to analyze the frequency and disturbances in rhythm at which PD or HD patients tap in response to a set frequency of the external cue.

In this context, it is necessary to understand what frequency means with respect to a tapping task. Frequency is denoted in Hz for metronome-based tasks. 1 Hz is one cycle per second or 1000 milliseconds, and therefore an external cue of 1 Hz would beep every 1000 ms.

Though the ideal term here should be the inter-tap interval/ inter-rate interval, as the frequency of tapping is basically the time between two taps, which has been earlier defined as inter-tap interval, we shall use Hz as earlier studies refer to metronome based tasks in terms of Hz.

8.3.4 Simple reaction time task

Voluntary movement, its planning and execution, can be tested via the simple reaction time paradigm. The stages of processing involved in a simple reaction time task can be denoted as stimulus presentation, response preparation followed by response. The act of the response in the hand-tapping task also involves movement. Hence, reaction time can be summed as response preparation time combined with movement time.

A stimulus is presented to which the individual responds. The time taken to do so is calculated as the simple reaction time. The stimulus may be an auditory or visual cue, prior to which the individual has received instructions or training. The time duration of the stimulus presentation can be varied, and gap paradigms can be included, in which a gap may or may not be allowed between the presentation of the target and the disappearance of the fixation area. Further details are provided under the description of the simple reaction time task used in our study.

8.3.5 Choice reaction time task

Choice reaction time tasks are similar to the simple reaction time task, in which a command is given to react in a certain way to a given stimulus. The individual is required to make a choice regarding the response to the given stimulus. These tasks, involve stimulus presentation, stimulus identification, stimulus response mapping, response selection, response programming and response initiation. An example of a choice reaction time task is the anti-tap task, wherein the movement required is in the opposite direction to the stimulus presented. However, since the instruction to tap on the opposite side has already been given, the response selection component will be eliminated, as there is a need for response inhibition (prevent oneself from tapping on the target that appears) and it will be a part of the processing required in preparation of the response.

Choice reaction time tapping tasks have been very few in PD and HD. Our study as described earlier involves an anti–tap task which is a choice reaction time task.

Previously documented studies show simple reaction time is longer in PD patients versus controls (Montgomery & Nuessen, 1990, Viallet et al, 1987, Jahanshi et al, 1992). Serial reaction time (SRT) has been found to be longer in HD patients (Knopman et al, 1991, Kim et al, 2004). In my literature review, I did not find specific studies relating to differentiation among PMG and MG subjects, in SRT and Choice reaction tasks (CRT). It would be interesting to study

differences in SRT and CRT in PMG, early and late MG, as well as in early and late PD.

8.3.6 Conflict task

Increasing cognitive load through second-order conditional rule tasks is hypothesized to be of greater difficulty in subjects with BG disorders (Robert et al, 2009). Saccadic versions of this paradigm have been shown to have greater latencies in HD subjects. These tasks have a mixture of pro- and anti-saccade tasks, with saccadic direction implied by the presence of an additional visual cue. Similar hand tapping tasks have not been performed before. Using a similar principle to pro- and anti–saccade, and an additional visual cue, a hand tapping task can be designed which can serve as a second order conditional rule task, which was attempted in our pilot study.

The conflict task is similar to a choice reaction task, however an additional cue directs the individual's choice. In a saccadic task, it requires the individual to look at or away from the stimulus presented depending on the visual cue. Instead of directly looking at or away from the stimulus, the subject is required to make a choice on the basis of the information provided by the visual cue, thus increasing the cognitive load. This test may be helpful in picking up early cognitive impairment. Though saccadic pathways are different from those involved in tapping, the ability to perform the voluntary action required can still be tested under similar conditions.

8.4 Rationale in using an Android tablet and JAVA programming

Tapping devices used at present, either test tapping or reaction time tasks, but not both. The devices used are expensive, bulky and the data may not always be reproducible. As a result, its clinical use is severely limited. Instead of developing a new tool for the purpose, we decided to leverage some of the features already existing in Android devices, and create an application for the Android ecosystem, which could be reused in other devices after sufficient testing. For this endeavor, we narrowed down on a Samsung Galaxy 7" tablet.

The app included both tapping and reaction time tasks, which was installed on the device. The measurements used were specific to the Samsung Galaxy, with the capability of extending it to other Android devices.

Android is an open source mobile Operating System created by Google Inc. Currently; it has the second largest market penetration after Apple iOS devices, in the mobile segment in US, and much higher penetration in developing countries. Being open source, mobile devices with Android operating system are generally much cheaper. Security was of utmost importance since we are dealing with clinical data. Since Android OS provides an application sandbox for every app, which isolates data from other apps, it limits the data availability to other applications on the mobile device, thereby providing a secure environment.

The application was programmed to be easily transferable and installed on Samsung Galaxy 7' tabs. Java is the default language of programming for creating Android applications.

Chapter 9

Results

9.1 Results: Group statistics

A pilot study was initially conducted which enabled me to identify useful measures for each test. It consisted of 6 PD, 5 HD patients and age matched controls.

The first part of the study consisted of 45 controls. This group was subdivided into 3 groups of controls consisting of:

1. 20 – 30 year olds
2. 35 – 45 year olds
3. 65 – 80 year olds

Group	Number	Mean Age
20 -30	15	24.6
35 - 45	14	39.7
65 - 80	16	74.5

Table 9.1 The grouping of controls by age to study the effect of age on tapping patterns.

The first part of the study sought to compare age differences in test measures, as well as identify baseline values for various test measures.

The second part of the study sought to compare differences between PD patients and controls, and similarly between HD patients and controls.

1. 21 PD patients and 18 controls
2. 17 HD patients and 17 controls

Group	**Number**	**Mean Age**
PD patients	21	75.9
Controls	18	76.3

Table 9. 2 Mean age and number of PD patients and controls

Group	**Number**	**20-30s (2)**	**35-45 (9)**	**65-75 (6)**
HD patients	17	27	36.9	74.2
Controls	18	25	34.2	75.7

Table 9.3 Mean age and number of HD patients and age matched controls

As outlined earlier, there were 5 tests, and each includes separate measures.

Both hands were tested, but patients and controls had a less than optimal performance with their non-dominant hand. However, there was no significant difference between the three groups of controls in terms of performance of the dominant or non – dominant hand. All measures and tests illustrated from here on are those of the dominant hand.

First task: Single finger tapping

The measures found to be the most promising from the pilot study were:

1. Total number of taps - Tap D (as they were performed by the dominant hand)
2. Mean inter-tap interval – ITI D
3. Inter-tap interval standard deviation – ITI SD
4. Mean force
5. Mean displacement from the central target – Displacement
6. Displacement SD
7. Error Count

Second task: Double target tapping

1. Taps on the right target – Taps R
2. Taps on the left target – Taps L
3. ITI
4. ITI SD

Third task: Metronome based task

Frequency of each block

1. With the external cue – Block frequency
2. Without the external cue – Rest frequency

The patterns generated were varied but the variables did not identify a significant difference in any particular block, though the controls always tapped at mean frequencies which were closest to the actual frequencies when compared to the patients. It is beyond the scope of this study to detail each of the 10 mean frequencies from the 3 experiments.

Fourth task: Pro-tap task

1. Simple reaction time – RT4
2. Standard deviation of RT4 – RT4 SD

Fifth task: Anti-tap task

1. Choice reaction time –RT5
2. Standard deviation of RT5 – RT5 SD

Sixth task: Conflict task

1. Reaction time – RT6
2. Standard deviation of RT6- RT6 SD

The parameters derived from the conflict task gave identical results as the anti and pro tap tasks, and therefore the testing was discontinued after the pilot study.

The other parameters outlined above are described as obtained from the three experiments performed are described.

9.2 **Hand tapping across age groups**

1. Taps D

Taps D	20 -30	35 -45	65 - 80
Mean	154.2	152.2	138.8
Std Deviation	12.44	12.71	23.6
Median	156	148	132
Std Error	3.21	3.39	5.9
Minimum	123	135	94
Maximum	171	174	173
Range	48	39	79

Table 9.4 Effect of age on tap counts using the dominant hand across the different age groups

ANOVA between the three groups yielded a significant difference between the groups. The 20 -30 year olds had significantly higher tap values when compared to the 65 -80 year olds. The tap values of the 35 -45 year olds, though lower was not significantly lower than the 65 -80s groups.

GROUP 1	**GROUP 2**	**p-value**
20 - 30	35 -45	1. 000
20 - 30	65 -80	**0. 045**
35 - 45	65 -80	0.103

Table 9.5 ANOVA between groups, with a significant difference between 20-30 and 65-80 age groups

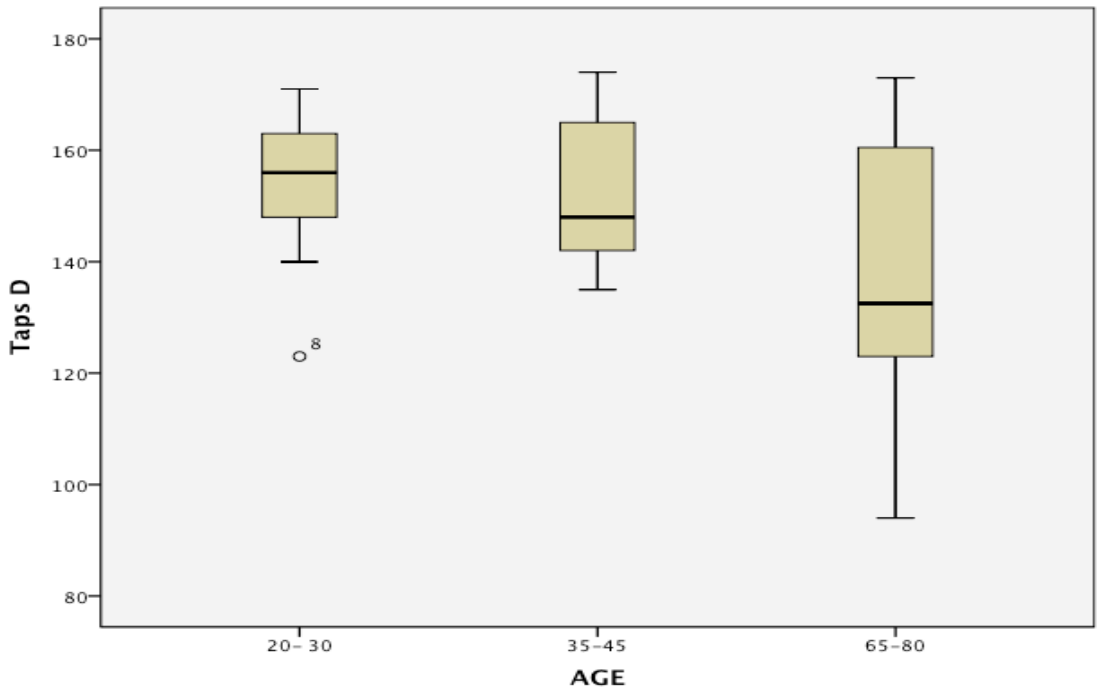


Fig 9.1 Box and whisker plots of tap counts between the groups. 65-80 group has the largest range, and a lower median value than the 20-30 and 35-45 group.

2. ITI D – Inter tap interval

ITI D	20 -30	35 -45	65 - 80
Mean	191.93	194.14	201.75
Std Deviation	15.41	35.27	35.27
Std Error	3.98	3.63	8.81
Minimum	174	174	164
Maximum	229	214	297
Range	55	40	133

Table 9.6 Effect of age on ITI on the dominant hand across the different age groups

ANOVA: Inter-tap interval between groups did not show any significant differences.

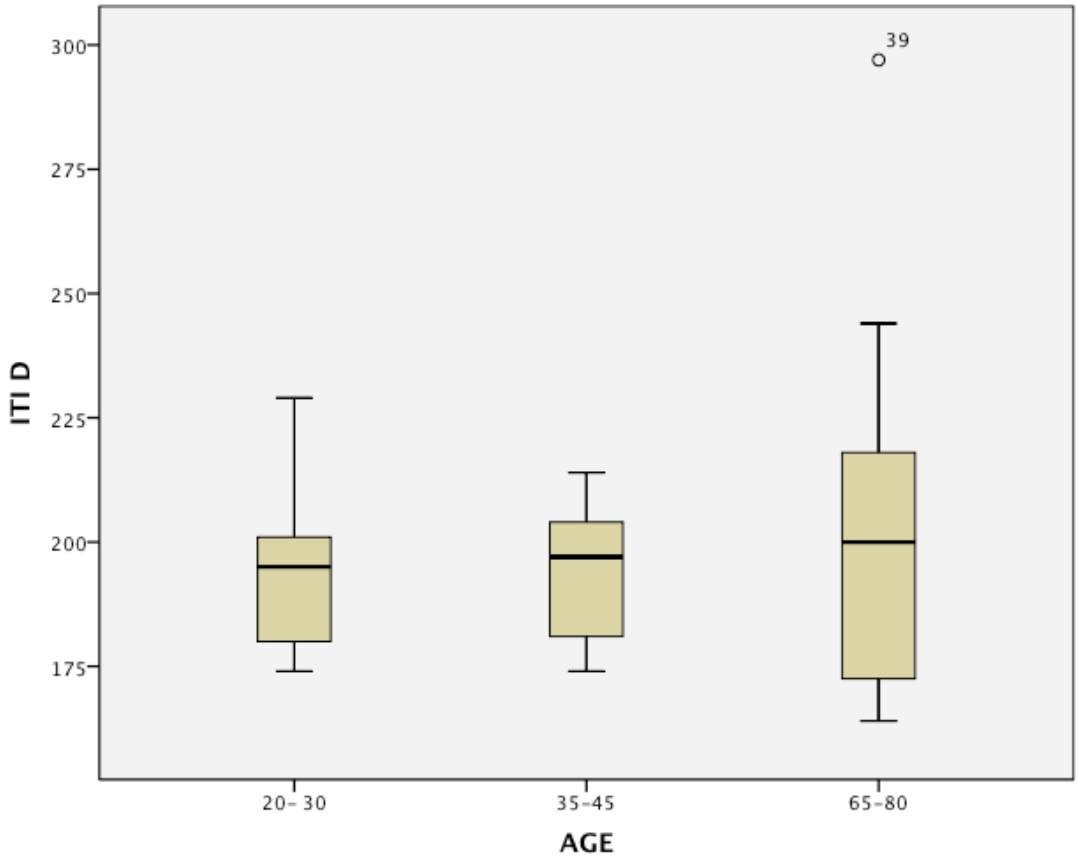


Fig 9.2: Box and whisker plots showing ITI across the three groups. Though the 65-80 groups show a higher range, the mean value is comparable to the 20-30 and 35-45 groups.

2. ITI SD - Inter-tap-interval (Standard deviation)

ITI SD	20 -30	35 -45	65 - 80
Mean	27.7	33.4	37.7
Std Deviation	19.3	21.8	26.1
Std Error	4.9	5.8	6.5
Minimum	9.17	13.9	13.2
Maximum	90.6	92.9	101.8
Range	81.5	79.0	88.6

Table 9.7: Effect of age on ITI SD of the dominant hand across different age groups

ANOVA and Non Parametric tests showed that there was no significant difference between the groups for this measure. The range of 65 – 80s group is higher than the other groups.

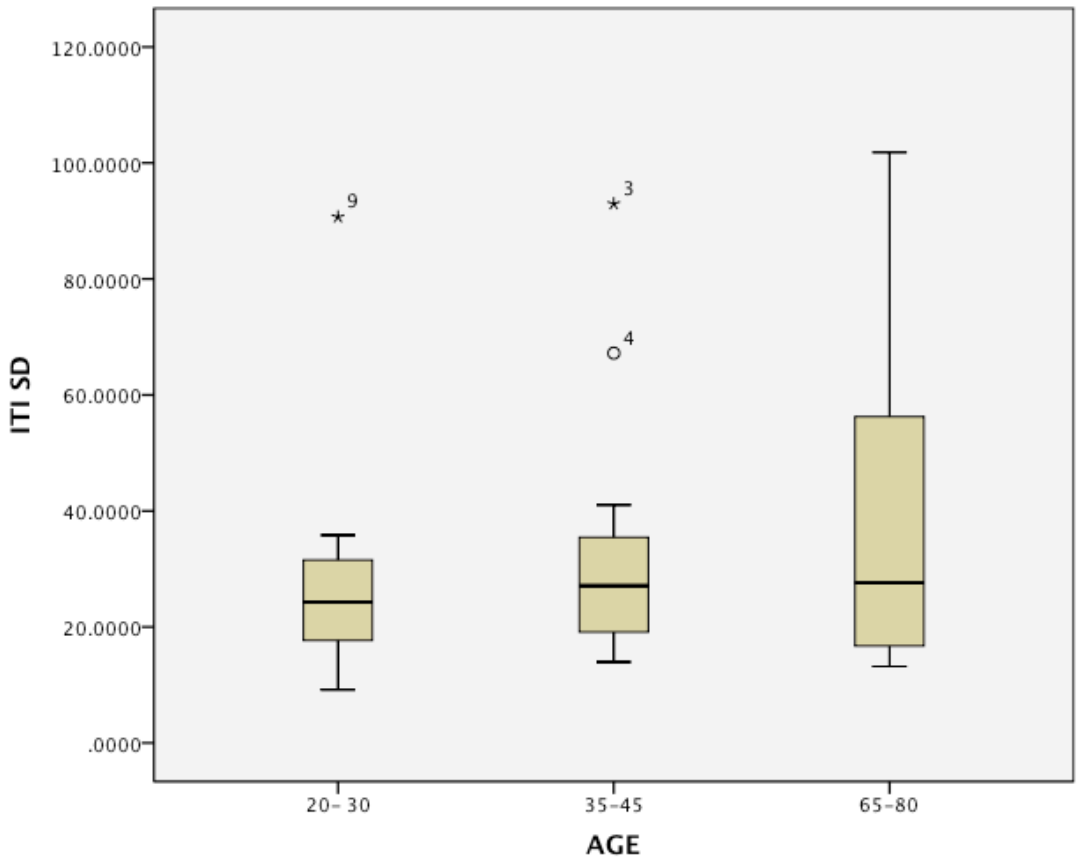


Fig 9.3 Box and whisker (BW) plots of ITI SD of the dominant hand shows a larger range for the 65-80s group, with the mean being comparable to other groups.

3. Force

Force D	20 -30	35 -45	65 - 80
Mean	9.59	9.54	9.5
Std Deviation	0.21	0.14	0.22
Median	9.62	9.55	9.55
Std Error	0.05	0.03	5.9
Minimum	9.17	9.31	9.0
Maximum	9.87	9.74	9.89
Range	0.7	0.43	0.89

Table 9.8 Effect of age on tapping force on the dominant hand across different age groups

ANOVA did not show a significant difference between the three groups, though the range of the 65 -80s group is higher. The median value of the 20s is higher than the other groups, but an overall comparison did not show a specific difference in tapping forces between groups.

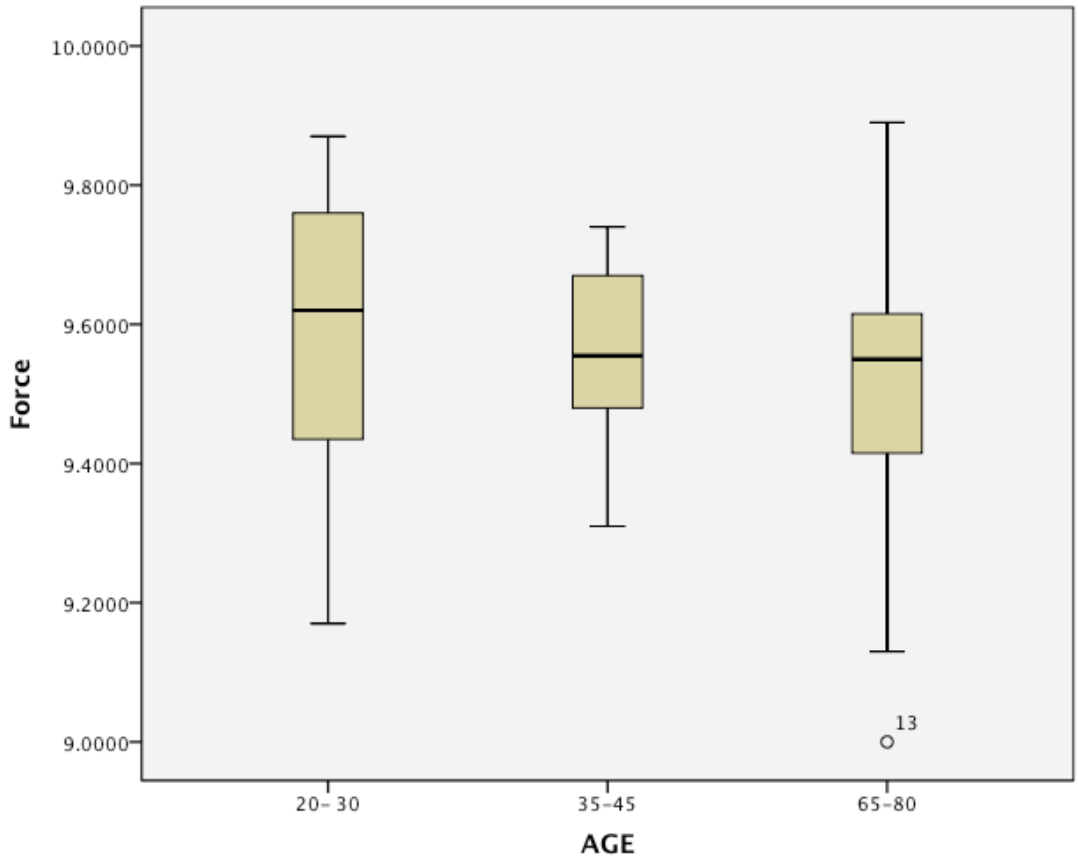


Fig 9.4 BW plots of force of the dominant hand among different age groups, showing a larger range of tapping forces in the youngest age group (20-30s).

4. Displacement

Displacement	20 -30	35 -45	65 - 80
Mean	1.18	1.24	2.74
Std Deviation	0.3	0.28	2.72
Median	1.1	1.26	2.23
Std Error	0.07	0.075	0.68
Minimum	0.7	0.82	0.59
Maximum	1.83	1.85	12.48
Range	1.05	1.03	11.8

Table 9.9 Effect of age on displacement from the target in the tapping task performed by the dominant hand across the different age groups

ANOVA, NPT and Post hoc Bonferroni reveal that there are significant differences between the groups for displacement. 20 – 30s group had smaller displacement values, which are considered the baseline, as it would not be possible to tap at the exact origin. Deviations from that center were larger, and progressively increased according to age in the 35 -45 and 65 –80s groups.

GROUP 1	GROUP 2	p-value
20 - 30	35 -45	1.000
20 - 30	65 -80	**0.034**
35 - 45	65 -80	**0.049**

Table 9.10 ANOVA between groups for displacement shows significant difference in tapping accuracy between all groups except between 20-30 and 35-45.

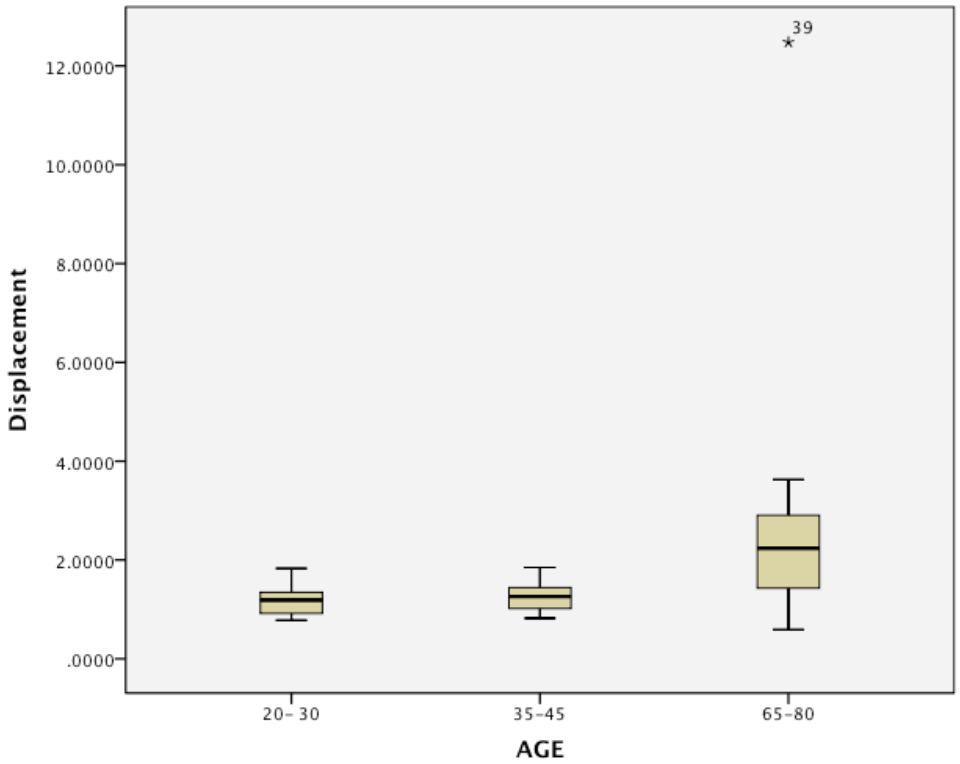


Fig 9.5 BW plots show a larger range of displacement in the 65-80s group, with minimal variation in the 20-30s and 35-45s groups indicating higher accuracy

2. Alternate target tapping with the index finger

1. Taps R D – Taps on the Right target with the dominant hand

Taps R D	20 -30	35 -45	65 - 80
Mean	42.2	40.57	36.44
Std Deviation	8.09	0.28	6.9
Median	42.06	40.0	35.5
Std Error	2.09	2.10	1.7
Minimum	28	30	25
Maximum	59	57	53
Range	31	27	28

Table 9.11 Effect of age on tap count on the right target across the different age groups

Non-parametric tests, ANOVA and post hoc Bonferroni revealed that there was no significant difference among the groups for this measure.

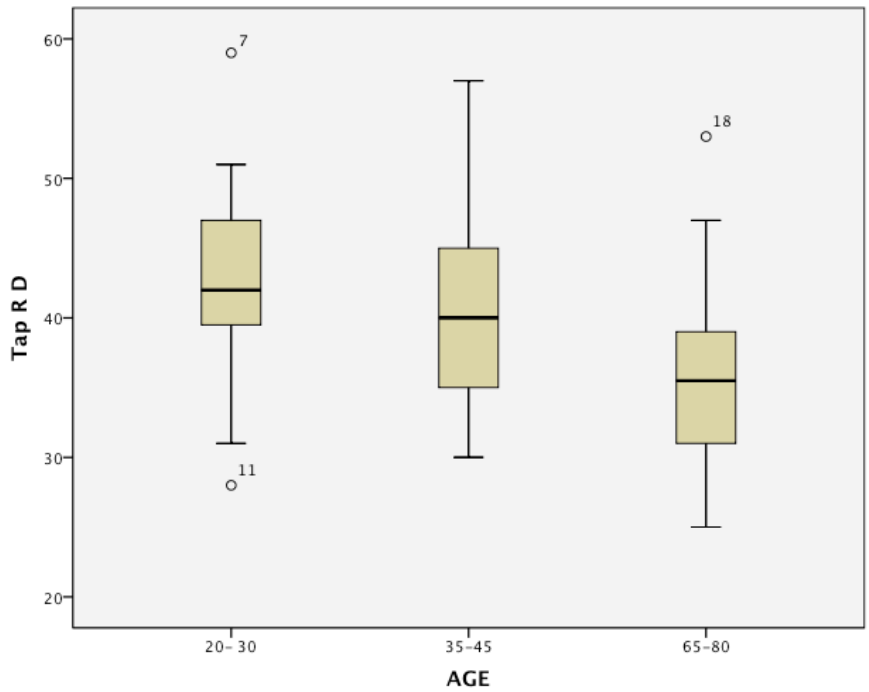


Fig 9.6: BW of Tap R across different age groups, shows a lower tap count in the 65-80s group.

1. Taps L D – Taps on the Left target using the Dominant Hand

Taps L D	20 -30	35 -45	65 - 80
Mean	42.13	40.57	35.88
Std Deviation	8.07	7.76	6.17
Median	41	39	36
Std Error	2.08	2.07	1.54
Minimum	27	30	25
Maximum	59	57	48
Range	32	27	23

Table 9.12 Effect of age on tap count on the left target across the different age groups

Non-parametric tests, ANOVA and Post Hoc Bonferroni revealed that there was no significant difference among the groups for this measure.

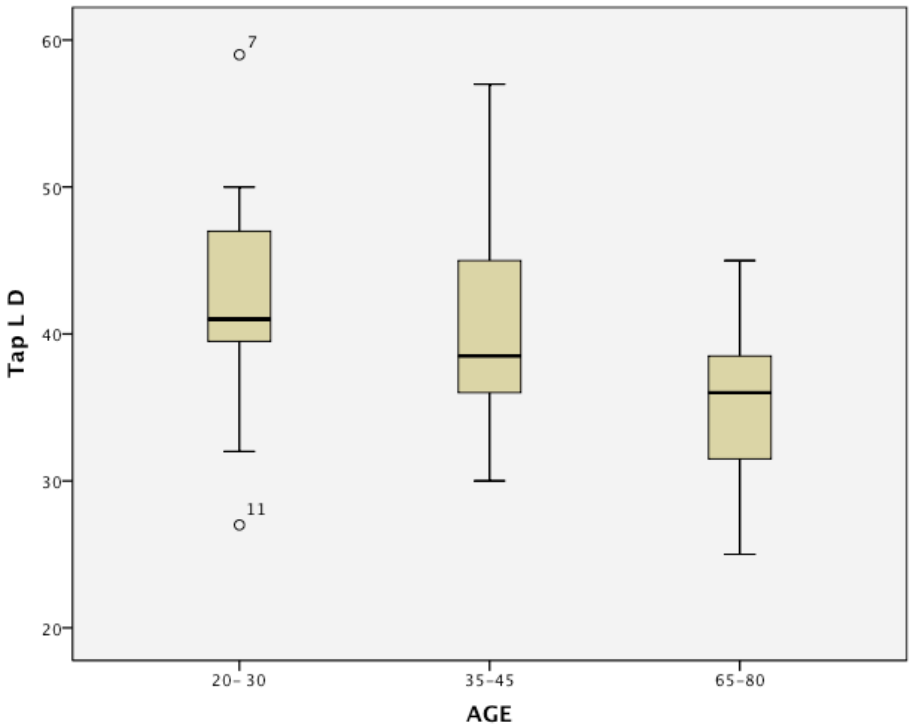


Fig 9.7: BW of Tap L showing lower tap counts in 65-80s group

2. ITI D - Inter-tap-interval (dominant hand)

ITI D	20 -30	35 -45	65 - 80
Mean	337.53	384.79	408.5
Std Deviation	83.48	68.5	66.3
Median	323	376	295
Std Error	21.5	18.3	16.5
Minimum	245	255	295
Maximum	523	483	578
Range	278	228	283

Table 9.13 Effect of age on ITI in the double target task across the different age groups

Non-parametric tests, ANOVA and Post Hoc Bonferroni reveal that there is a significant difference among groups for this measure. The median and ranges of ITI values among 35 -45 year olds and 65 – 80s group were high, however only the ITI of 20s and 65 -80s were significantly different from each other.

GROUP 1	**GROUP 2**	**p-value**
20 - 30	35 -45	0.268
20 - 30	65 -80	**0.030**
35 - 45	65 -80	1.000

Table 9.14 Comparison of ITI between groups, showing a significant difference between 20-30 and 65-80s group.

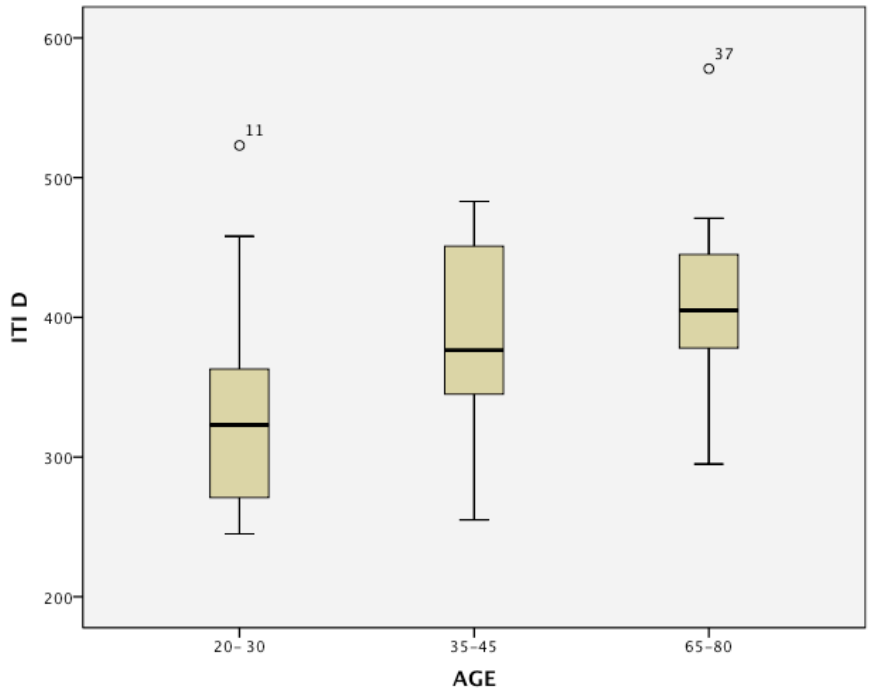


Fig 9.8 BW plots showing higher ITI in the 65-80s age group, and larger range of ITI in the 20-30s group.

5. ITI SD - Inter-tap-interval standard deviation

ITI SD	20 -30	35 -45	65 - 80
Mean	38.3	39.9	48.6
Std Deviation	13.3	10.2	23.7
Median	39.6	38.4	38.3
Std Error	3.45	2.7	5.9
Minimum	23.2	25.4	22.4
Maximum	66.2	57.1	108.0
Range	43	31.6	85.7

Table 9.15: Effect of age on SD of ITI across the different age groups

Non-parametric tests and Post Hoc Bonferroni show that there are no significant differences between groups for this measure.

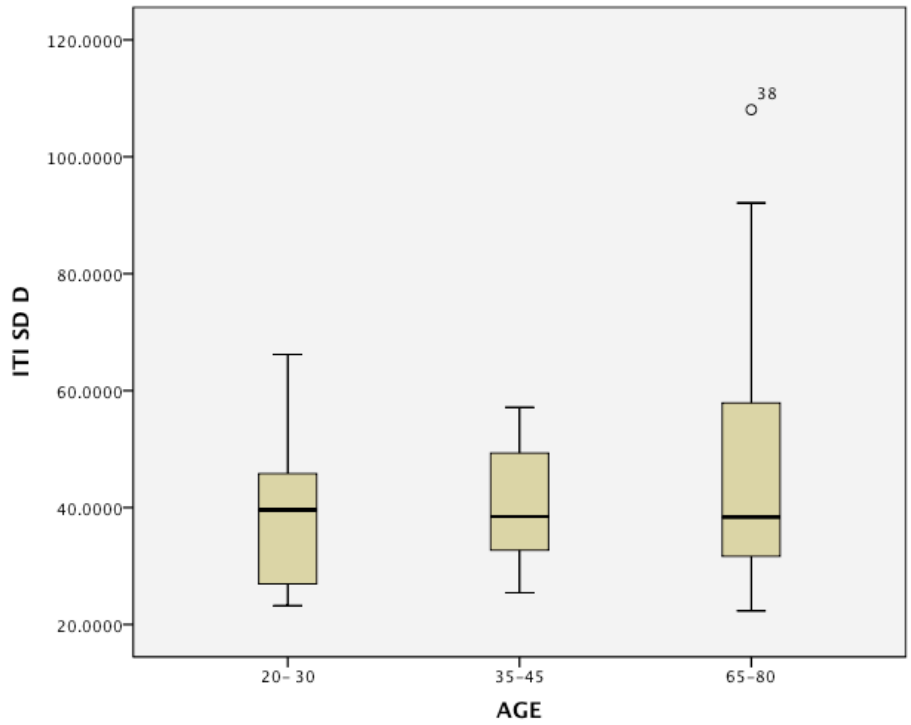


Fig 9.8 BW plots of ITI SD showing a larger range of ITI in the 65-80s group

4. Reaction time task - Simple reaction time

1. RT4 D – Reaction Time (dominant hand)

RT D	20 -30	35 -45	65 - 80
Mean	484.6	503.6	617.2
Std Deviation	41.5	22.4	111.8
Median	483	507.5	596.5
Std Error	10.7	6.0	27.9
Minimum	427	472	502
Maximum	568	557	934
Range	141	87	432

Table 9.16 Effect of age on simple reaction time across the different age group

Non-parametric, ANOVA and Post Hoc Bonferroni show that there are significant differences in reaction time between the groups.

Non-parametric tests showed a significant p- value of **0.04** across all groups.

Post Hoc Bonferroni

GROUP 1	**GROUP 2**	**p-value**
20 - 30	35 -45	1.000
20 - 30	65 -80	**0.000**
35 - 45	65 -80	**0.001**

Table 9.17 Comparison of RT4 D among groups showing a significant difference between 65-80s with other groups.

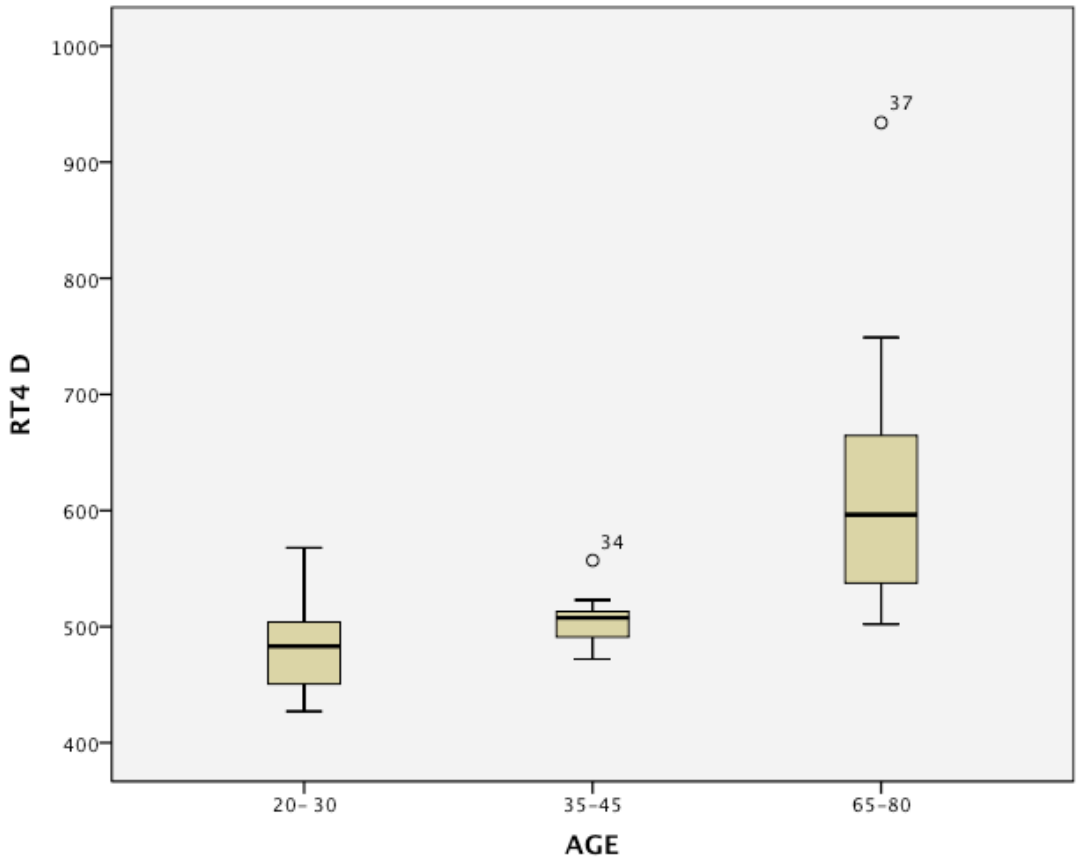


Fig 9.9 BW plots showing increasing RT4 values across the groups.

2. Reaction time standard deviation – RT4 SD

RT4 SD	20 -30	35 -45	65 - 80
Mean	41.7	47.3	98.0
Std Deviation	16.2	15.4	89.6
Median	35.6	47.8	67.4
Std Error	4.18	4.13	22.4
Minimum	24.9	24.5	32.4
Maximum	91.6	75.1	393
Range	66.7	50.6	360.5

Table 9.18 Effect of age on SD of RT4 D across the different age groups

Non-parametric tests show a significant difference between groups, with a p – value of 0.003

Post hoc Bonferroni

GROUP 1	**GROUP 2**	**p-value**
20 - 30	35 -45	1.000
20 - 30	65 -80	**0.02**
35 - 45	65 -80	**0.047**

Table 9.19: Comparison of standard deviation of RT4 D among groups showing a significant difference between 65-80s groups and others.

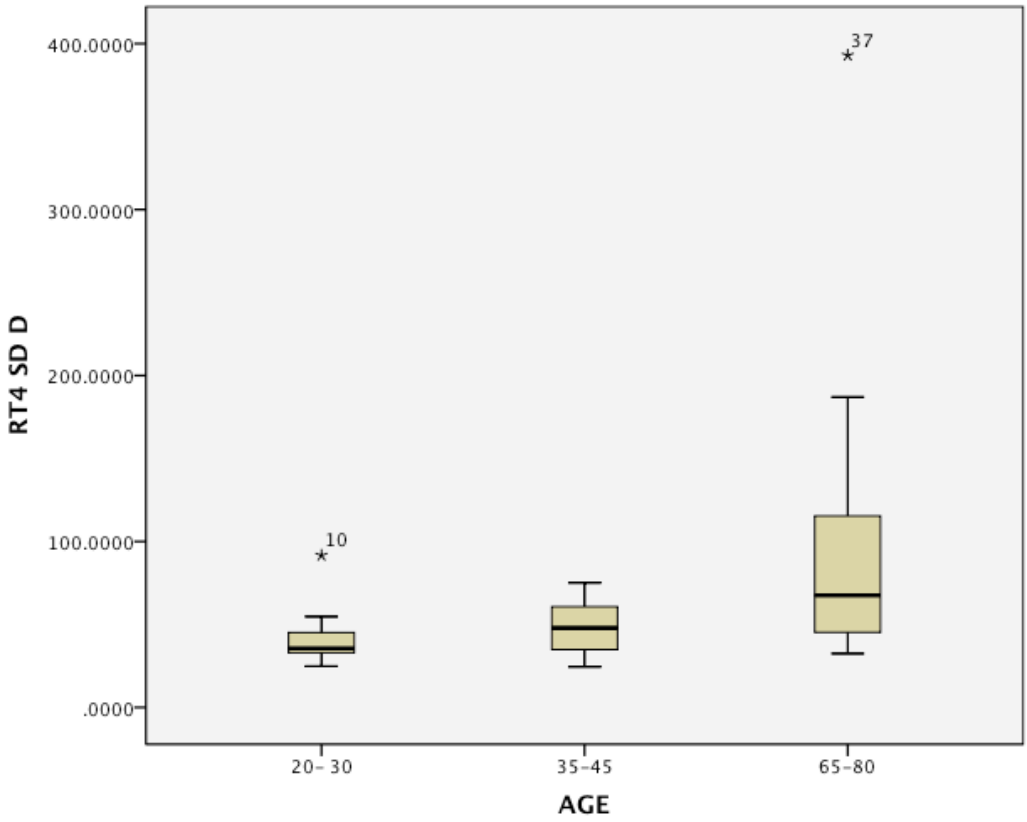


Fig 9.10 BW plots showing increasing SD of RT4 with increasing age and higher ranges in the 65-80s group

3. Reaction Time – Complex/ Anti tap task

    1. Choice reaction time (dominant hand) - RT5 D

RT5 D	20 -30	35 -45	65 - 80
Mean	511.5	590.7	783
Std Deviation	51.3	71.6	125.3
Median	511	605	793
Std Error	13.2	19.1	31.3
Minimum	442	481	598
Maximum	601	694	1105
Range	159	213	507

Table 9.20 Effect of age on RT 5 on the dominant hand across the different age groups

ANOVA revealed a significant difference among all groups, with a p – value of 0.000

There was no difference among and 20 -30s, and 35 -45 groups. 65–80s group had a significantly longer reaction time than the other groups.

Post-hoc Bonferroni

GROUP 1	**GROUP 2**	**p-value**
20 - 30	35 -45	0.067
20 - 30	65 -80	**0.000**
35 - 45	65 -80	**0.000**

Table 9.21 Comparison of RT5 among groups shows a significant difference between 65-80s group and others

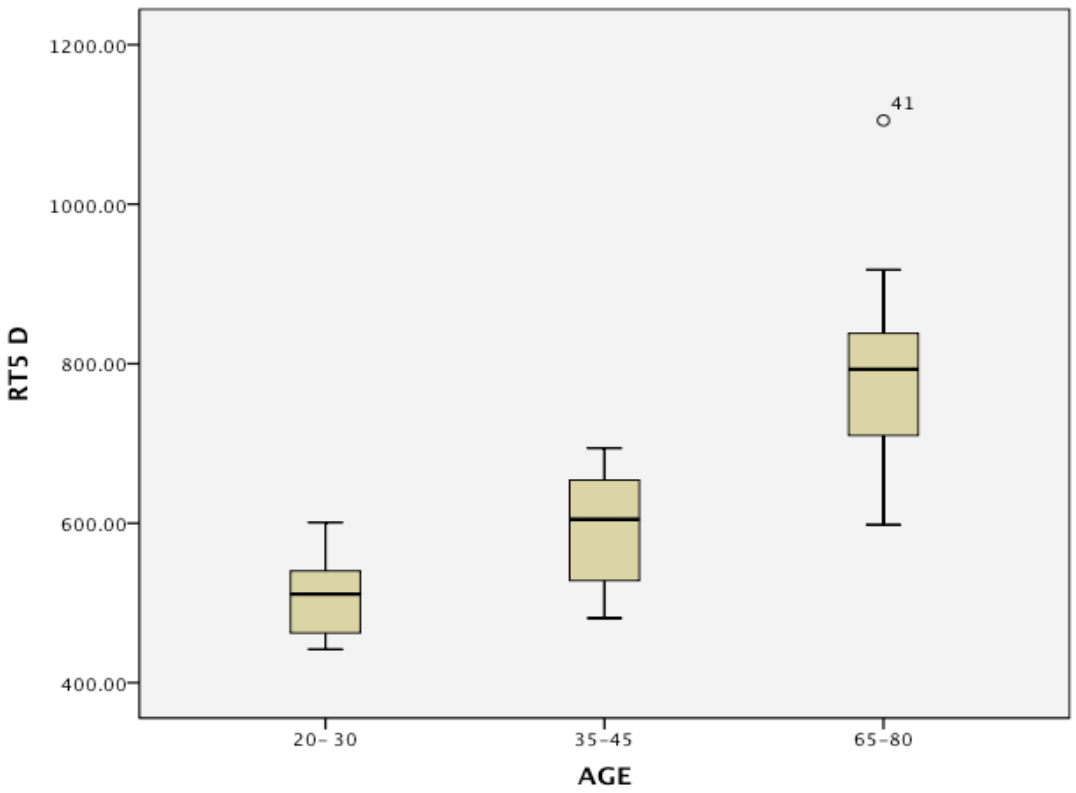


Fig 9.11 BW plots of RT5 showing increasing with age, with 65-80s having the longest reaction times and wider ranges.

2. Reaction time standard deviation – RT5 SD

RT5 SD	20 -30	35 -45	65 - 80
Mean	50.83	78.67	130.3
Std Deviation	17.7	32.5	57.67
Median	50.8	75.3	124.7
Std Error	4.59	8.68	14.4
Minimum	24.4	41.5	59.3
Maximum	97.9	170.8	281.1
Range	73.5	129.2	221.7

Table 9.22 Effect of age on SD of RT5 across the different age groups

ANOVA showed a significant difference in reaction time among the different groups, with a p – value of 0.000

Individual comparison shows that there was no significant difference between 20- 30s and 35 -45 groups. However, 65 -80s had a significantly different SD of reaction time when compared to the other two groups.

Post hoc Bonferroni

GROUP 1	**GROUP 2**	**p-value**
20 - 30	35 -45	0.20
20 - 30	65 -80	**0.000**
35 - 45	65 -80	**0.003**

Table 9.23 Comparison of groups showed a significant difference in SD of RT5 between 65-80s and other groups

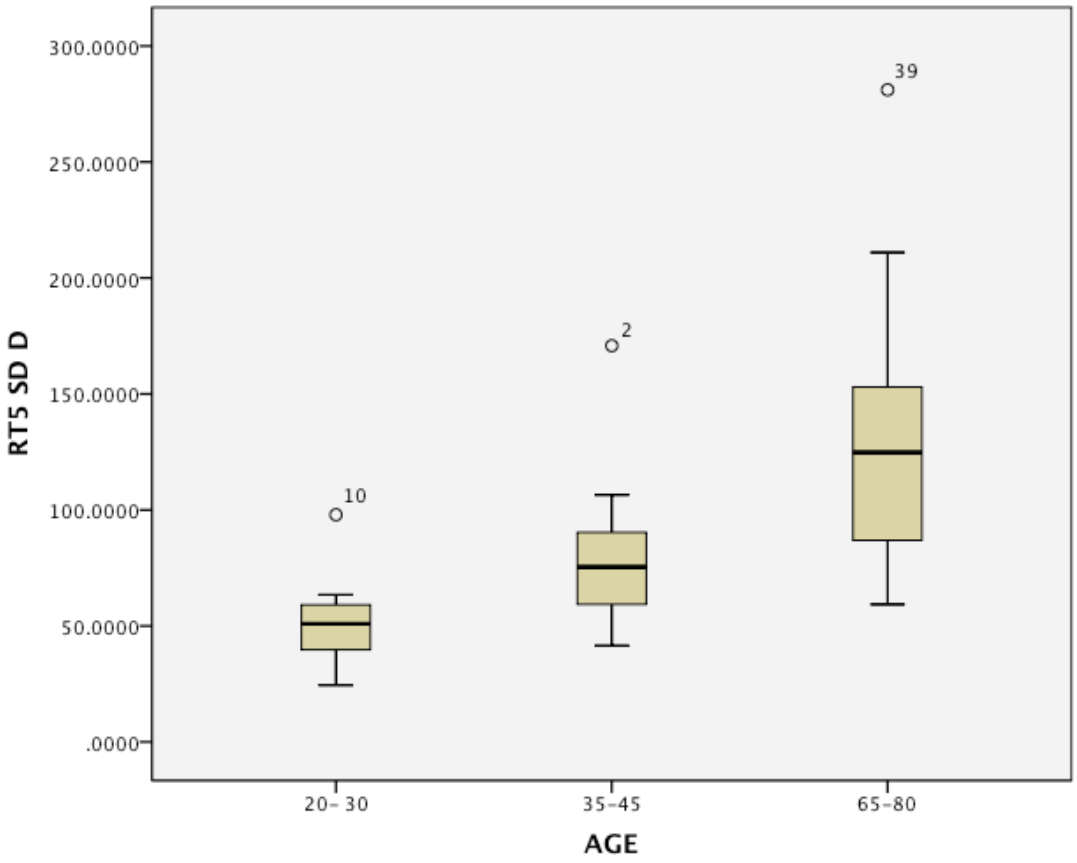


Fig 9.12: BW plots of SD of RT5 showing longer SDs of RT5 in 65-80s with wider ranges.

9.3 Comparison of hand tapping in PD patients versus controls

1. Self paced or fast tapping

1. Taps D - Total tap count (dominant hand)

Taps D	PD	Controls
Mean	130	140
Std Deviation	30.5	24.2
Median	132	133
Std Error	6.6	5.23
Minimum	63	94
Maximum	174	173
Range	111	79

Table 9.23: Comparison of tap count parameters between PD subjects and controls

As the data was not normal, NPT was performed, and Mann – Whitney gave a p-value of 0.002 and showed a significant difference between PD and controls for Taps with the dominant hand in the first task.

GROUPS	**Asmp. Sig (2 –tailed)**	**Exact sig. (1 – tailed)**
PD vs Control	0.002	0.002

Table 9.24: Comparison of Taps D showed a significant difference between PD and controls.

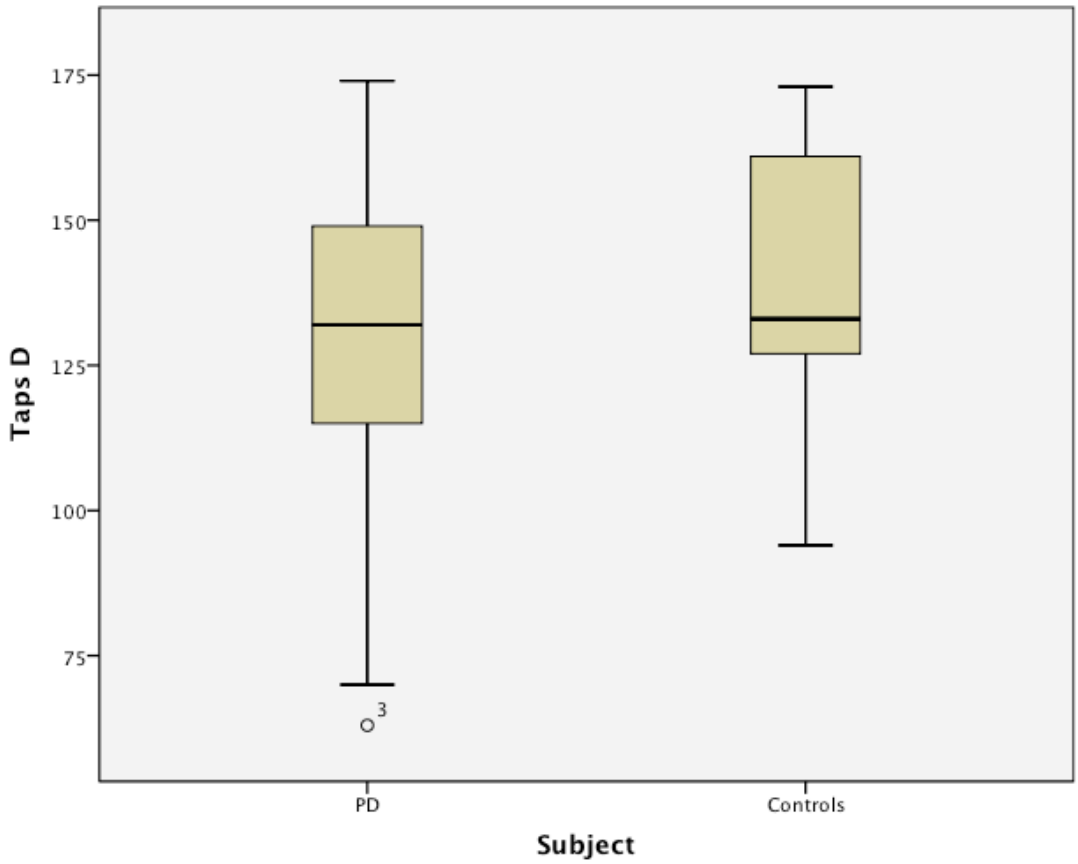


Fig 9.13 BW plots of Taps D showing higher tap counts among controls

2. ITI D

ITI D	PD	Controls
Mean	231.19	199.71
Std Deviation	71.4	35.17
Median	219	197
Std Error	15.5	8.5
Minimum	166	164
Maximum	456	297
Range	290	133

Table 9.25 Comparison of ITI parameters between PD subjects and controls

A t-test was performed on the data, which gave a non significant p-value of 0.106, showing no significant difference between PD and controls for Inter-tap intervals.

GROUPS	Equal Variances assumed (2 –tailed)	Equal variance not assumed (1 – tailed)
PD vs Control	0.106	0.087

Table 9.26 Comparison of ITI - No significant difference between PD subjects and controls

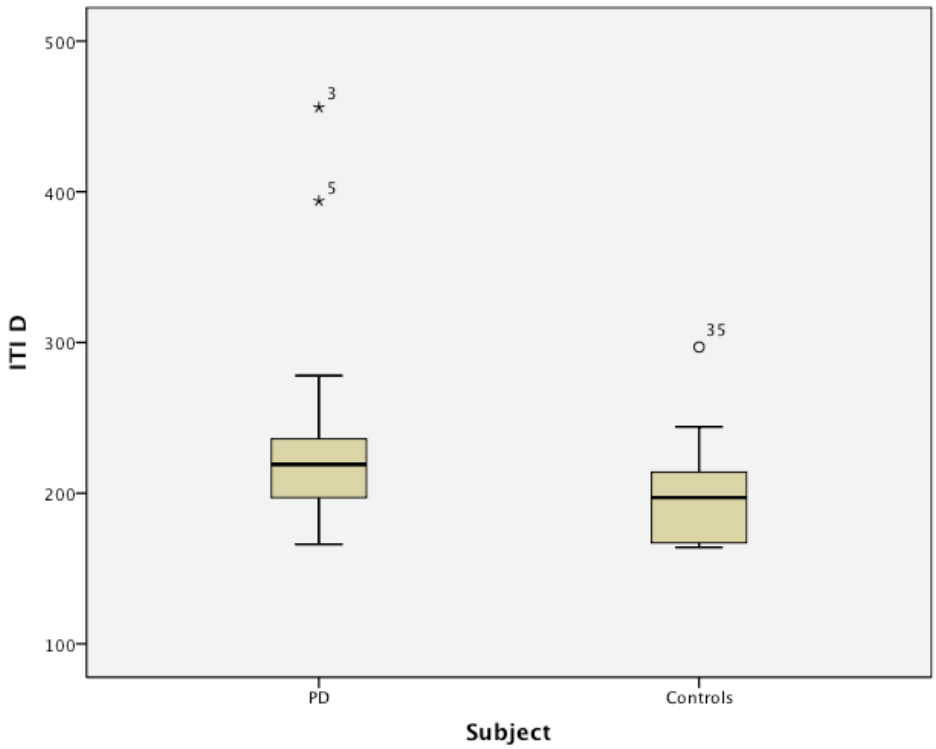


Fig 9.14 BW plots of ITI of PD and controls showing lower ITI among controls.

3. ITI SD

ITI SD D	PD	Controls
Mean	57.19	38.46
Std Deviation	62.43	25.51
Median	27	29
Std Error	13.6	6.18
Minimum	8.22	13.2
Maximum	249.15	101.8
Range	240.9	88.64

Table 9.27 Comparison of SD of ITI between PD subjects and controls

T- test did not show any significant difference between PD and Controls

GROUPS	**Equal variance assumed (2-tailed)**	**Equal variance not assumed (2-tailed)**
PD vs Control	0.254	0.221

Table 9.28 Comparison between PD and groups – No significant difference with t-tests

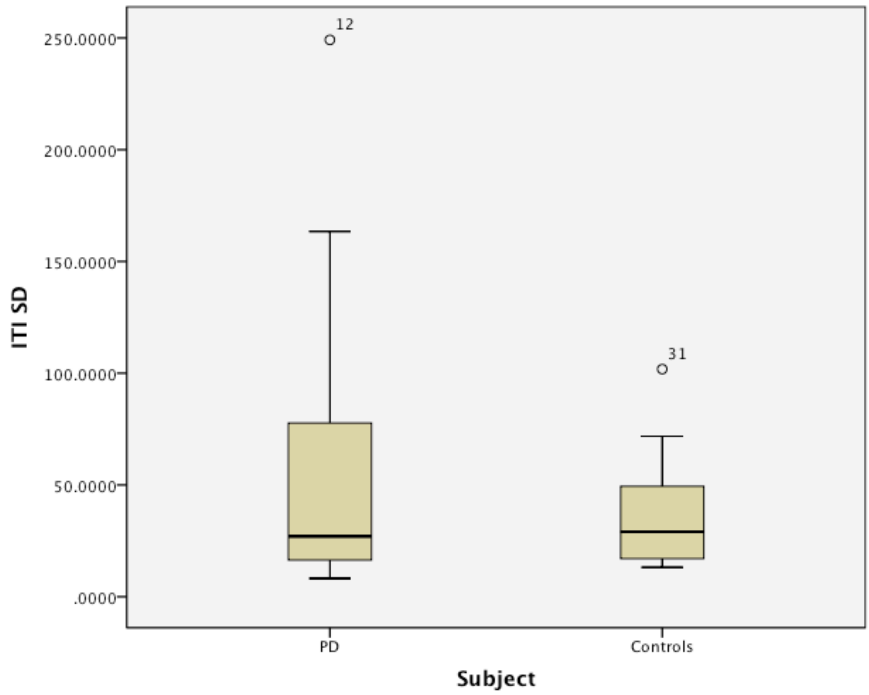


Fig 9.15 BW plots of ITI SD showing larger SD of ITI among PD patients.

4. Force D – Tapping force (dominant hand)

Force D	PD	Controls
Mean	9.52	9.51
Std Deviation	0.18	0.22
Median	9.52	9.59
Std Error	0.04	0.54
Minimum	9.27	9
Maximum	9.83	9.89
Range	0.56	0.89

Table 9.29 Comparison of tapping force between PD subjects and controls

As the data was not normal, NPT was performed, and Mann – Whitney gave a p-value of 0.735 and showed no significant difference between PD and controls for tapping force with the dominant hand for the first task.

GROUPS	**Asmp. Sig (2 –tailed)**	**Exact sig. (1 – tailed)**
PD vs Control	0.735	0.750

Table 9.30 Comparison of tapping force showing no difference between PD subjects and controls

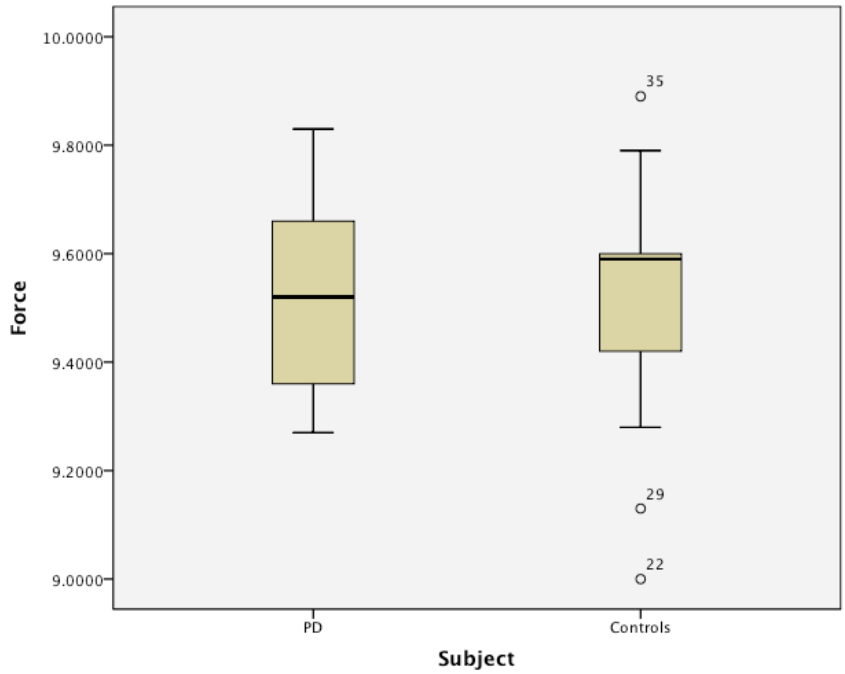


Fig 9.16 BW plots of Force D showing a wider range among PD patients

5. Displacement D

Displacement D	PD	Controls
Mean	3.15	1.73
Std Deviation	2.03	3.21
Median	2.24	0.72
Std Error	0.44	0.78
Minimum	0.98	0.31
Maximum	8.55	13.6
Range	7.5	13.2

Table 9.31 Comparison of displacement between PD subjects and controls

As the data was not normal, NPT was performed, and Mann–Whitney gave a p-value of 0.000 and showed a significant difference between PD and controls for displacement with the dominant hand for the first task.

GROUPS	Asmp. Sig (2 –tailed)	Exact sig. (1 – tailed)
PD vs Control	0.000	0.001

Table 9.32: Comparison of displacement showing a significant difference between PD subjects and controls

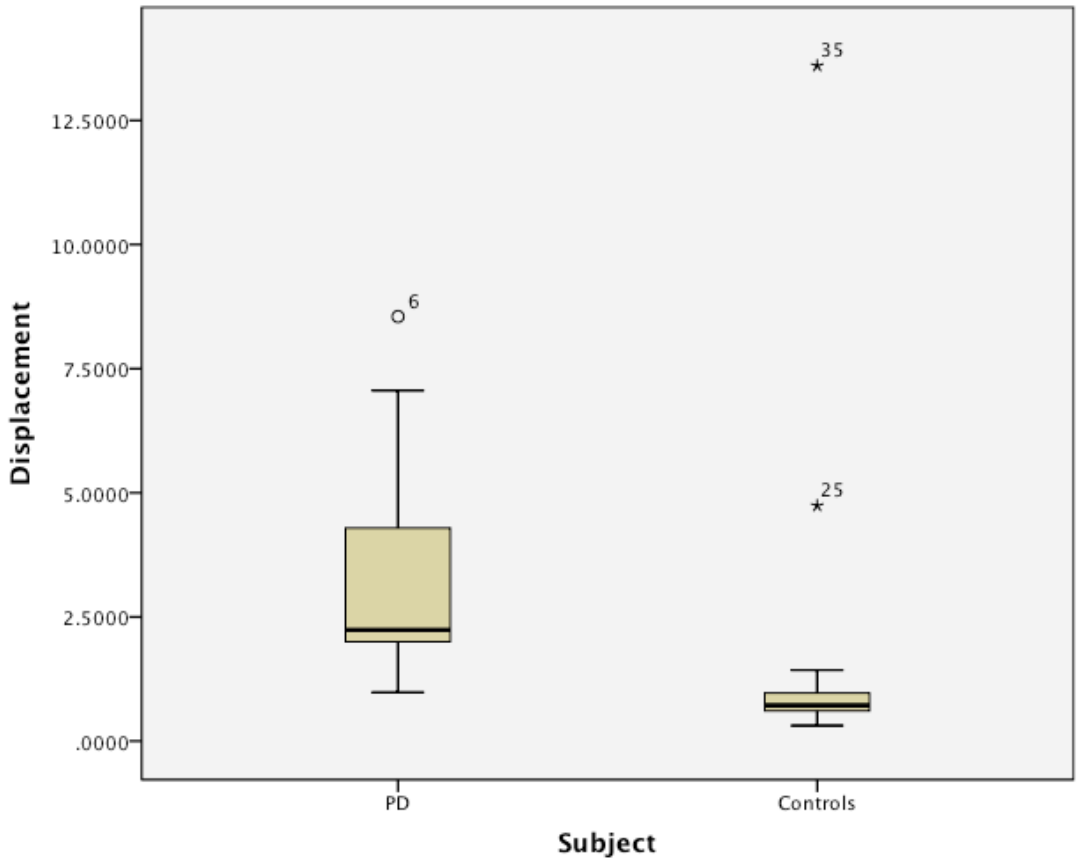


Fig 9.17 BW plots showing larger displacement or lower accuracy values among PD patients.

2. Task 2 – Double target finger tapping

1. Taps L D

Tap Count on the left target – Dominant hand

Taps L D	PD	Controls
Mean	26	36
Std Deviation	7.68	5.4
Median	26	36
Std Error	1.7	1.3
Minimum	12	25
Maximum	39	45
Range	27	20

Table 9.33 Comparison of Taps L between PD and controls

As the data was not normal, NPT was performed, and Mann – Whitney gave a p-value of 0.000 and showed a significant difference between PD and controls for taps on the left target with the dominant hand on for the first task.

GROUPS	**Asmp . Sig (2 –tailed)**	**Exact sig. (1 – tailed)**
PD vs Control	0.000	0.000

Table 9.34 Comparison of Taps L showing a significant difference between PD and controls

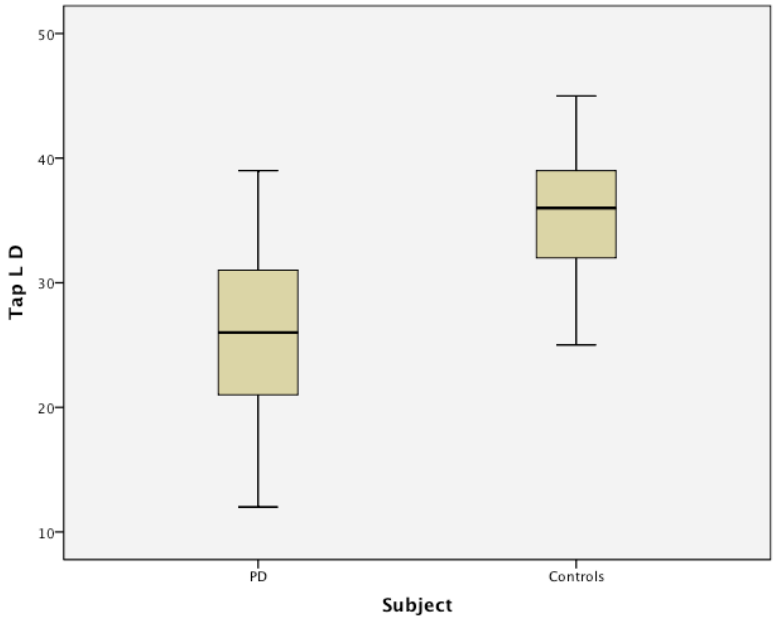


Fig 9.18 BW plots of Taps L showing lower tap counts among PD patients

2. Taps R D

Taps L D	PD	Controls
Mean	26	37
Std Deviation	7.82	6.7
Median	26	36
Std Error	1.7	1.6
Minimum	13	25
Maximum	39	53
Range	26	28

Table 9.35: Comparison of Taps R between PD and controls

As the data was not normal, NPT was performed, and Mann–Whitney gave a p-value of 0.000 and showed a significant difference between PD and controls for taps on the right target with the dominant hand for the first task.

GROUPS	Asmp . Sig (2 –tailed)	Exact sig. (1 – tailed)
PD vs Control	0.000	0.000

Table 9.36 Comparison of Taps R showing a significant difference between PD and controls

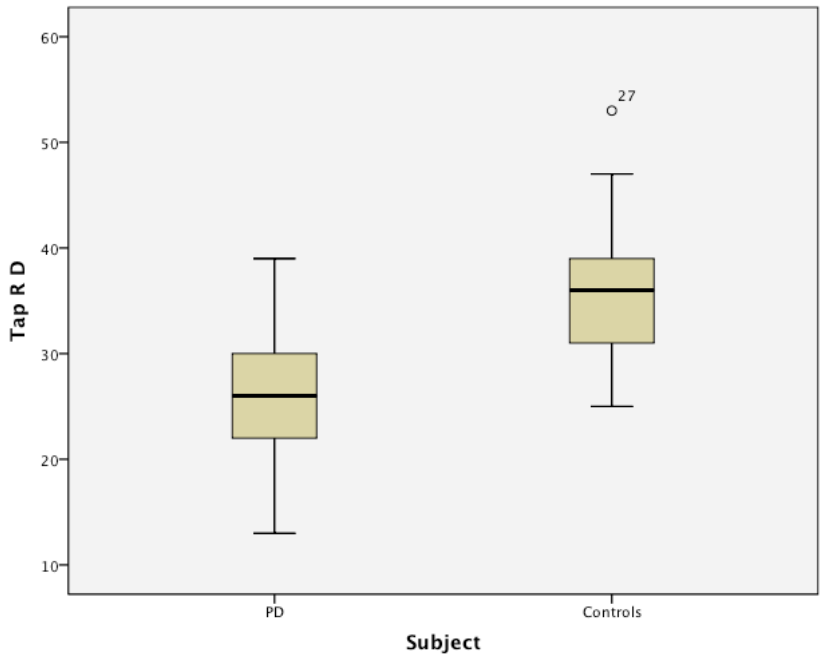


Fig 9.19: BW plots of Taps R showing lower tap counts among PD patients

3. ITI D

ITI – Inter-tap-intervals between double targets (Dominant hand)

ITI D	PD	Controls
Mean	597.6	406.2
Std Deviation	196	64.8
Median	557	404
Std Error	42.7	15.7
Minimum	375	295
Maximum	1103	578
Range	728	283

Table 9.37 Comparison of ITI D between PD and controls

As the data was not normal, NPT was performed, and Mann – Whitney gave a p-value of 0.000 and showed a significant difference between PD and controls for Inter tap interval with the dominant hand on the second task.

GROUPS	Asmp. Sig (2 –tailed)	Exact sig. (1 – tailed)
PD vs Control	0.000	0.000

Table 9.38 Comparison of ITI D showing a significant difference between PD and controls

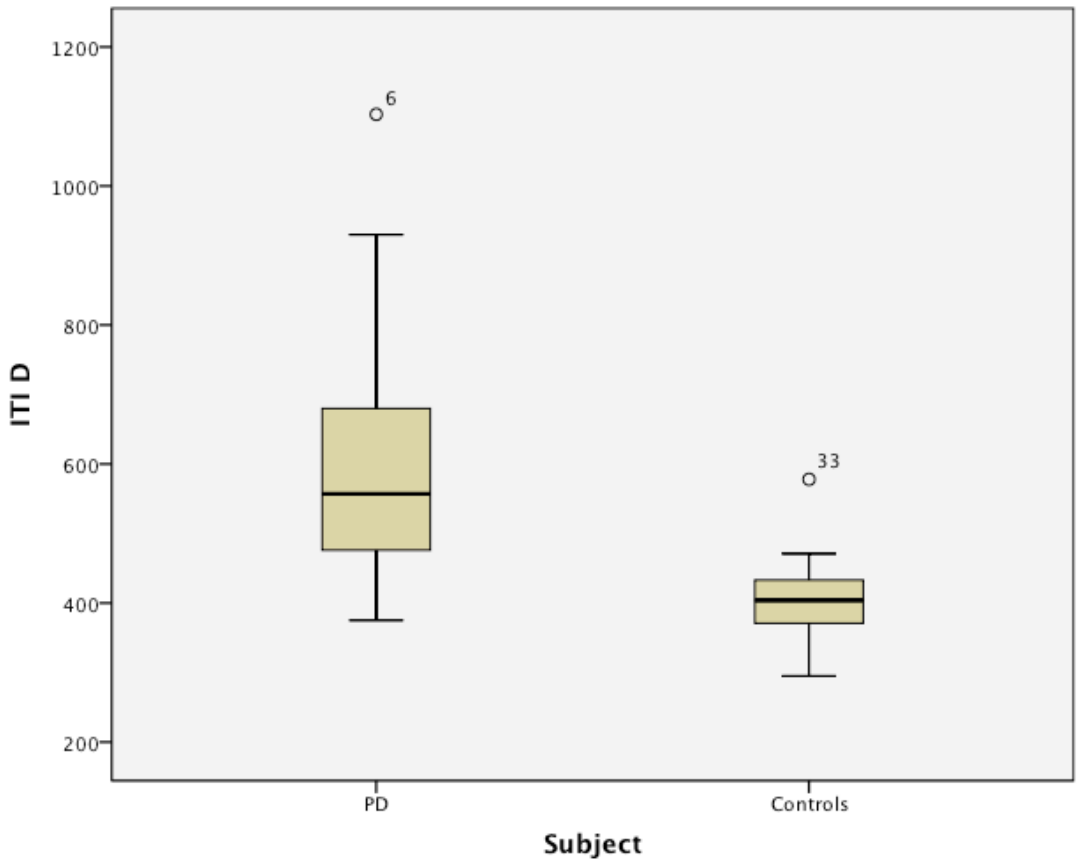


Fig 9.20 BW plots showing smaller ITI D among controls

4. ITI SD

Standard deviation of ITI (dominant hand)

ITI SD	PD	Controls
Mean	118.6	49.2
Std Deviation	136.1	23.1
Median	61.4	38.4
Std Error	29.7	5.6
Minimum	27.8	22.3
Maximum	576	108
Range	548.1	85.7

Table 9.39 Comparison of ITI SD between PD and controls

As the data was normal, ANOVA was performed, which showed a p-value of 0.000 and demonstrated a significant difference between PD and controls for Inter tap interval SD with the dominant hand for the second task.

GROUPS	**Equal Variances assumed (2 –tailed)**	**Equal variances not assumed (2 –tailed)**
PD vs Control	0.045	0.032

Table 9.40 Comparison of ITI SD showing a significant difference between PD and controls

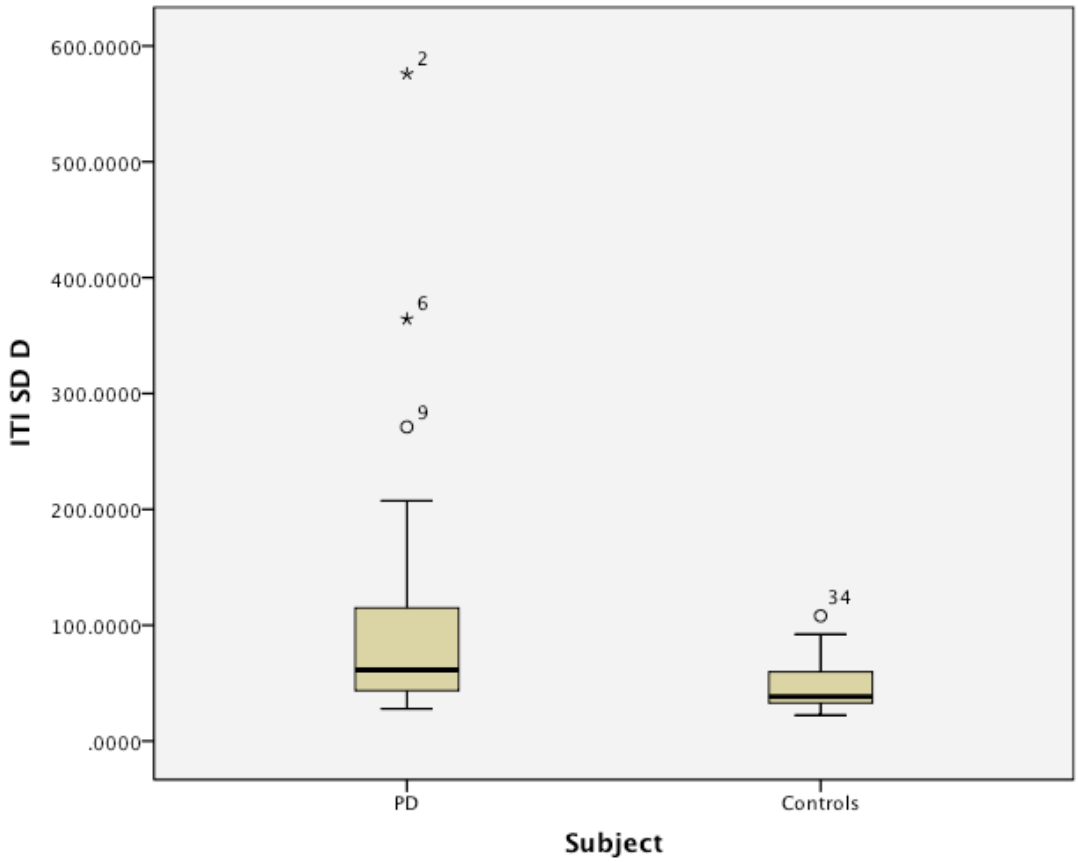


Fig 9.21 BW plots showing lower ITI SD among controls

5. Displacement R D

Displacement from central target on the right sensor (Dominant hand)

Displacement R D	PD	Controls
Mean	4.35	4.31
Std Deviation	2.1	1.9
Median	3.89	3.8
Std Error	0.45	0.47
Minimum	1.65	2.09
Maximum	9.8	9.5
Range	8.16	7.4

Table 9.41 Comparison of Displacement R D between PD and controls

As the data was normal, ANOVA was performed, which showed a p-value of 0.1 and demonstrated no significant difference between PD and controls for displacement with the dominant hand for the second task.

GROUPS	Equal Variances assumed (2 –tailed)	Equal variances not assumed (2 –tailed)
PD vs Control	0.955	0.955

Table 9.42 41 Comparison of Displacement R D showing no difference between PD and controls

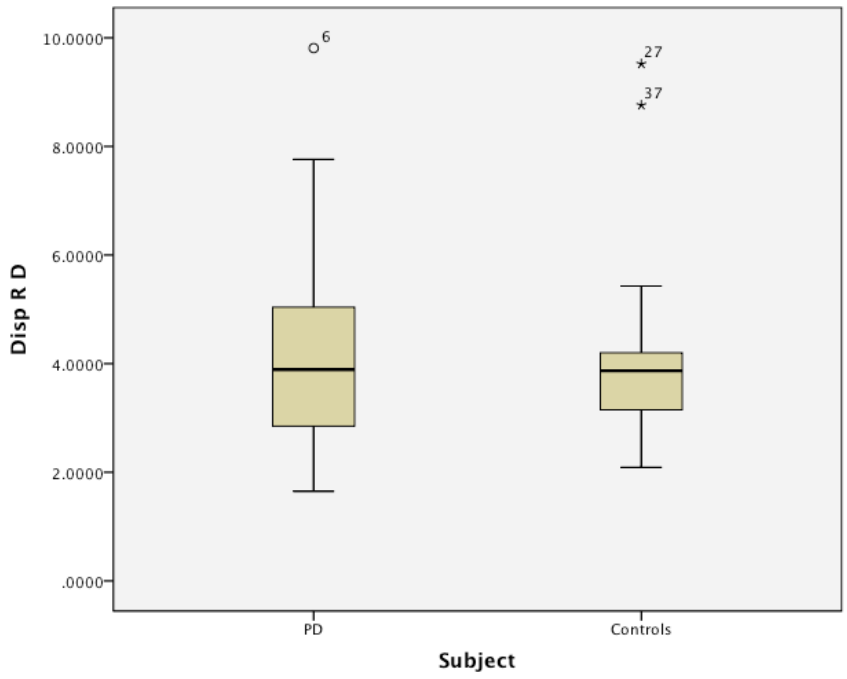


Fig 9.22 BW plots showing a wider range of Displacement R D among PD patients.

6. Displacement L D

Displacement L D	PD	Controls
Mean	5.33	4.02
Std Deviation	4.5	1.3
Median	3.87	3.8
Std Error	0.45	0.47
Minimum	1.08	1.89
Maximum	22.05	6.5
Range	20.9	4.7

Table 9.43 Comparison of Displacement L D between PD and controls

As the data was not normal, NPT was performed. Mann Whitney showed a p-value of 0.597 and demonstrated no significant difference between PD and controls for displacement with the dominant hand for the second task.

GROUPS	**Asymp Sig (2 –tailed)**	**Exact sig (2 –tailed)**
PD vs Control	0.597	0.601

Table 9.44 Comparison of Displacement L D showing no significant difference between PD and controls

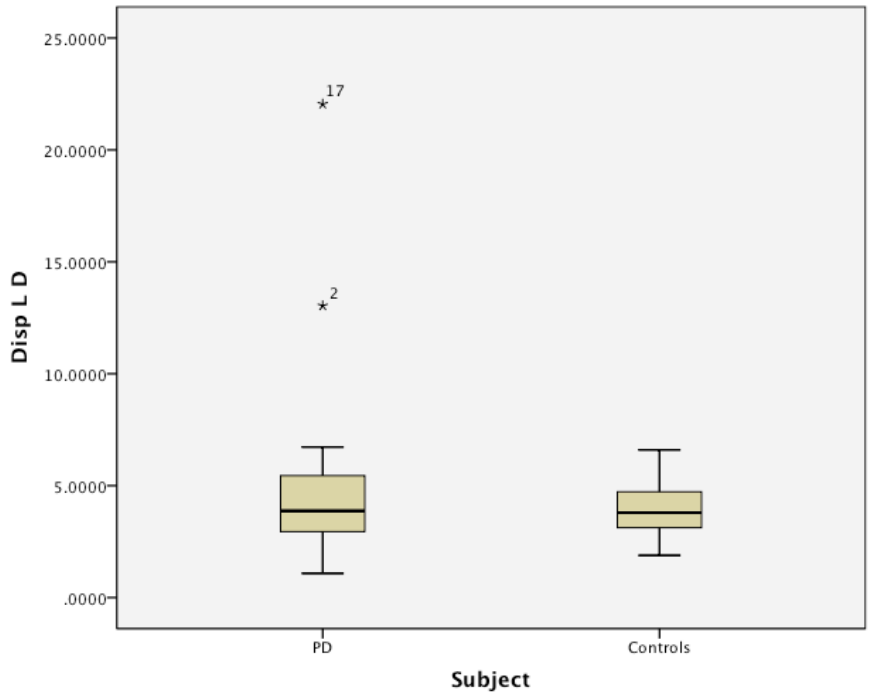


Fig 9.23 BW plots of Displacement L D showing wider range in PD patients, though the means are comparable.

3. Pro-tap Task

1. Reaction time – RT 4 D

Simple reaction time (Dominant hand) – RT 4 D

RT D	PD	Controls
Mean	792.7	614
Std Deviation	292	109
Median	724	586
Std Error	63.7	26.4
Minimum	485	502
Maximum	1655	934
Range	1170	432

Table 9.45 41 Comparison of RT4 D between PD and controls

As the data was normal, t-test was performed, which showed a p-value of 0.022 and demonstrated a significant difference between PD and controls for Reaction Time with the dominant hand for the fourth task.

GROUPS	Equal Variances assumed (2 –tailed)	Equal variances not assumed (2 –tailed)
PD vs Control	0.022	0.015

Table 9.46 Comparison of RT4 D showing a significant difference between PD and controls

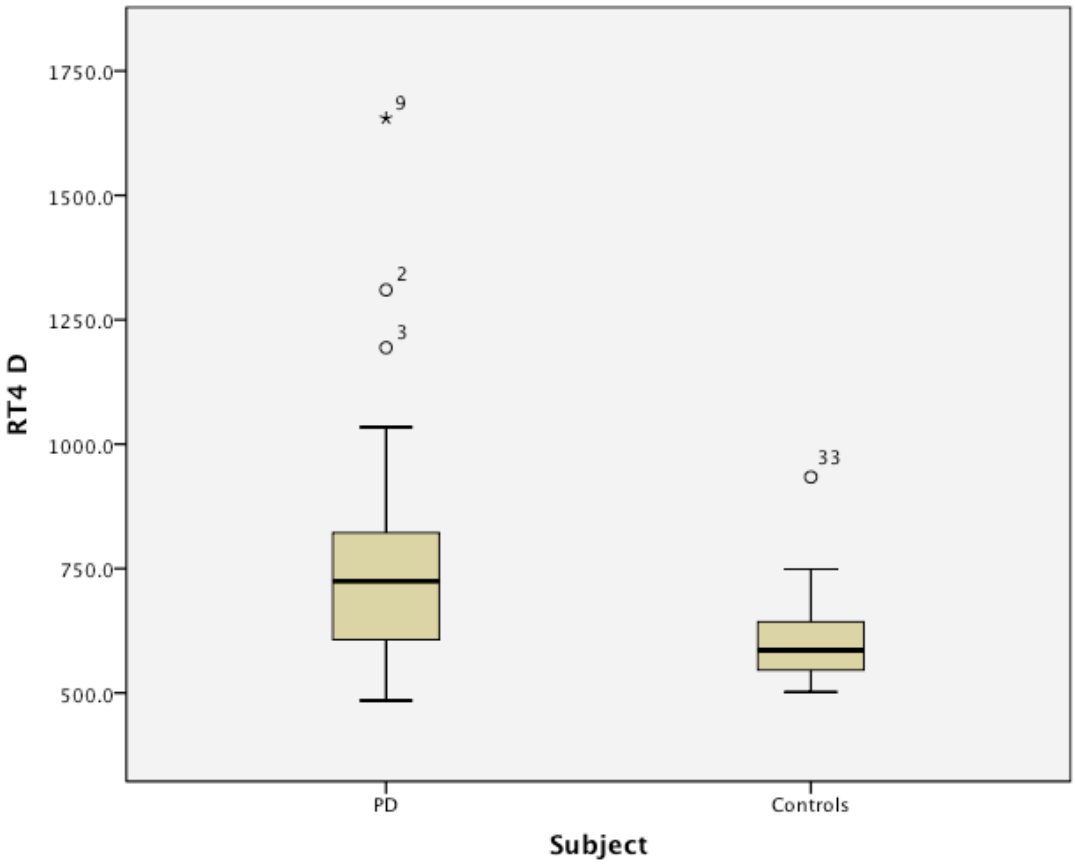


Fig 9.24 BW plots showing longer RT4 D among PD patients and some outliers, which are twice the mean RT.

2. Reaction Time SD – RT4 SD

Standard deviation of RT4 D (dominant hand)

RT4 SD	PD	Controls
Mean	176.5	84.7
Std Deviation	140.6	48.7
Median	114.8	81.8
Std Error	30.7	11.8
Minimum	44.8	32.4
Maximum	491.8	187
Range	446.9	154.5

Table 9.47 Comparison of RT4 SD between PD and controls

As the data was normal, t-test was performed, which showed a p-value of 0.015 and demonstrated a significant difference between PD and controls for the standard deviation of reaction time with the dominant hand for the fourth task.

GROUPS	**Equal Variances assumed (2 –tailed)**	**Equal variances not assumed (2 –tailed)**
PD vs Control	0.015	0.01

Table 9.48 Comparison of RT4 SD showing a significant difference between PD and controls

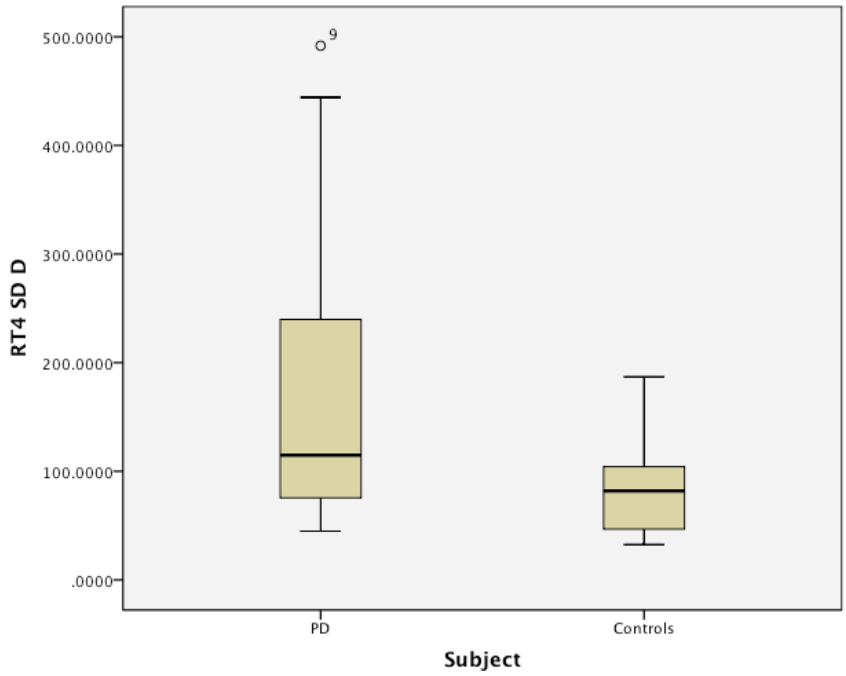


Fig 9.25 BW plots showing larger SD of RT4 and wider ranges in PD patients

4. Anti-tap task (Choice reaction time)

1. Reaction time 5 (RT 5 D)

Choice reaction time (Dominant hand)

RT5 D	PD	Controls
Mean	933.7	751.1
Std Deviation	232.2	96.4
Median	973.5	756
Std Error	51.9	23.3
Minimum	592	598
Maximum	1438	917
Range	846	319

Table 9.49 Comparison of RT5 D between PD and controls

As the data was not normal, NPT was performed, Mann-Whitney showed a p-value of 0.022 and demonstrated a significant difference between PD and controls for Standard Deviation of reaction time with the dominant hand for the fifth task.

GROUPS	Asymp Sig (2 tailed)	Exact Sig (1 –tailed)
PD vs Control	0.022	0.022

Table 9.50 Comparison of RT5 D showing a significant difference between PD and controls

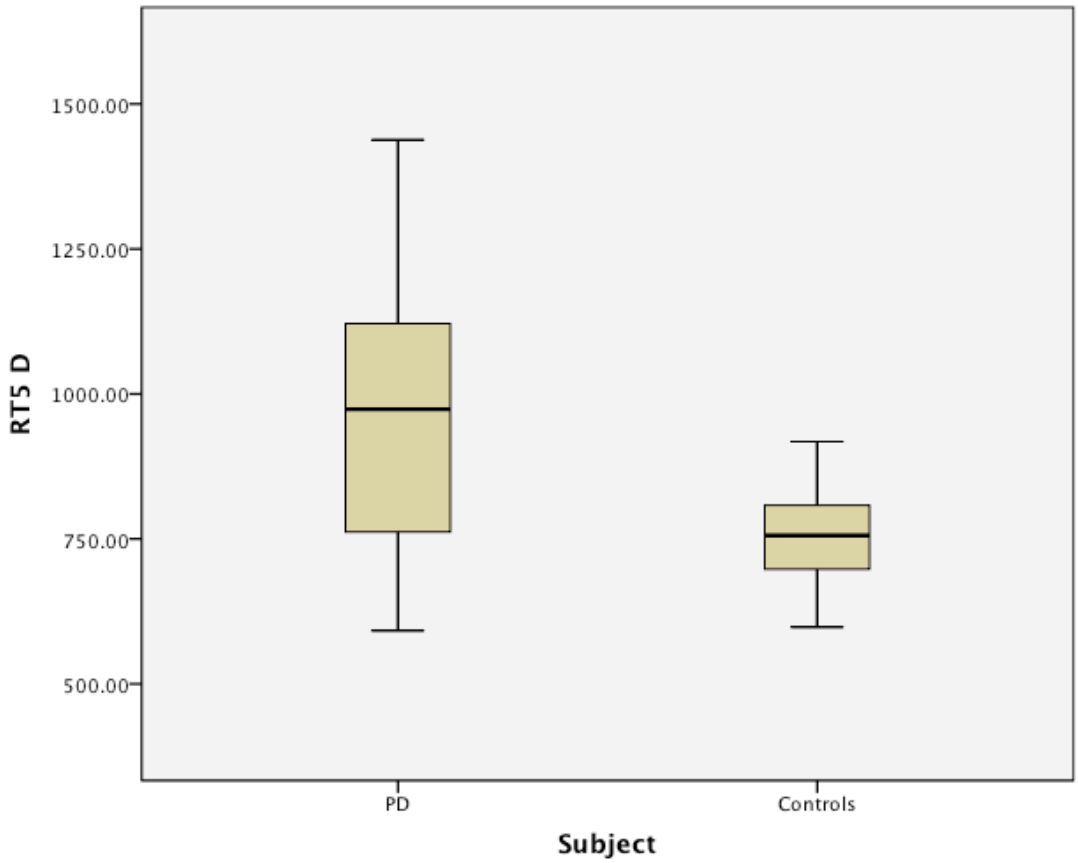


Fig 9. 26 BW plots showing longer RT5 D among PD patients and wider ranges.

2. Reaction time SD (RT5 SD)

Standard deviation of choice reaction time (Dominant hand)

RT5 SD	PD	Controls
Mean	322.7	129.1
Std Deviation	274.6	56.1
Median	213	117
Std Error	61.4	13.6
Minimum	95.6	59.3
Maximum	978	281.1
Range	882	221.1

Table 9.51 Comparison of RT5 SD between PD and controls

As the data was not normal, NPT was performed, Mann Whitney showed a p-value of 0.005 and demonstrated a significant difference between PD and controls for Standard Deviation of reaction time with the dominant hand for the fifth task.

GROUPS	**Asymp Sig (2 tailed)**	**Exact Sig (1 –tailed)**
PD vs Control	0.005	0.004

Table 9.52 Comparison of RT5 SD showing significant difference between PD and controls

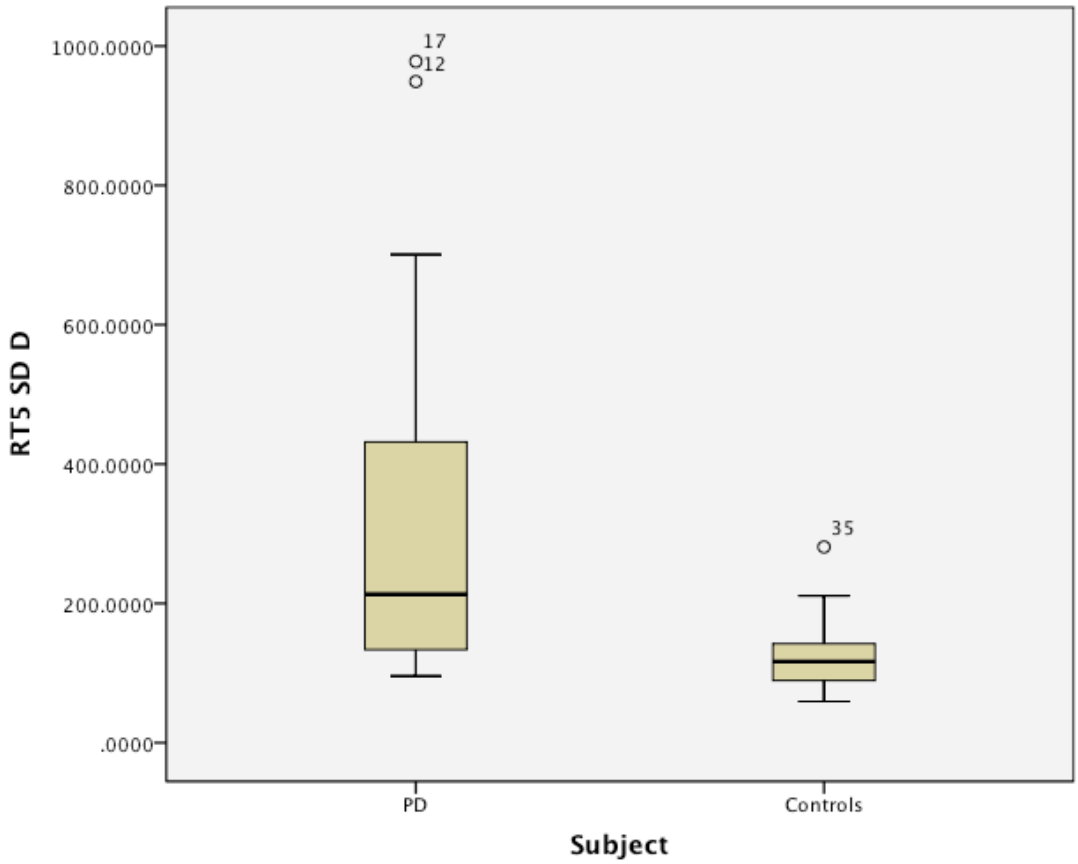


Fig 9.27 BW plots showing longer RT5 SD and wider ranges among PD patients

9.4 Comparison of hand tapping tasks between HD patients and controls.

1. Speeded or fast tapping

1. Taps D

Total tap count (dominant hand)

Taps D	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	105	132	122	147	99	138
Std Dev	30.4	12.0	40.1	11.4	33.6	27.9
Std Error	21.5	8.5	13.3	3.8	13.7	11.4
Median	105.5	132	136	146	88	130
Minimum	84	123	60	135	70	108
Maximum	127	140	168	167	162	173
Range	43	17	108	32	46	65

Table 9.53 Comparison of Taps D between HD and controls of the three age groups

Taps D for this group was non-normal data, and a non-parametric test (NPT), Kruskal-Wallis was used. The tapping rates of HD patients were not significantly different from the controls as the p-value was 0.11 on the KW test.

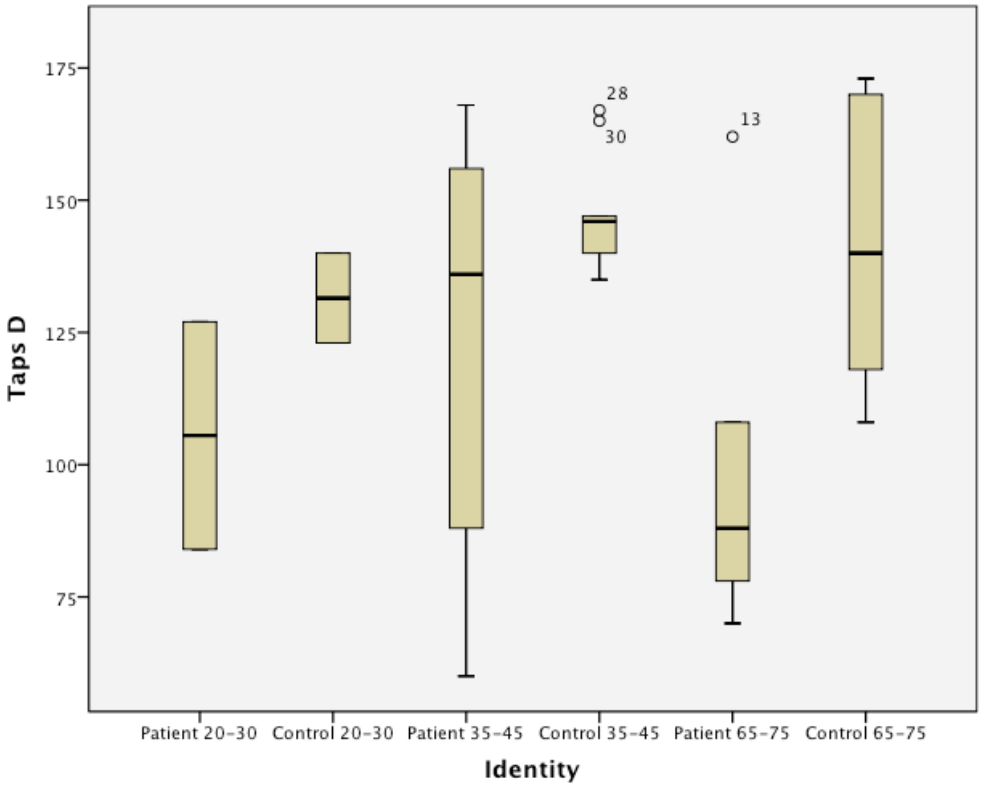


Fig 9.28 BW plots of the different groups showed the tap counts of patients were lower than controls and had wider ranges.

Ranks

	Identity	N	Mean Rank
Taps D	Patient 20-30	2	10.00
	Control 20-30	2	16.75
	Patient 35-45	9	16.50
	Control 35-45	9	23.00
	Patient 65-75	6	9.42
	Control 65-75	6	21.58
	Total	34	

Table 9.54 Ranking of Taps D of the different groups shows no significant difference among the 3 groups of HD vs controls

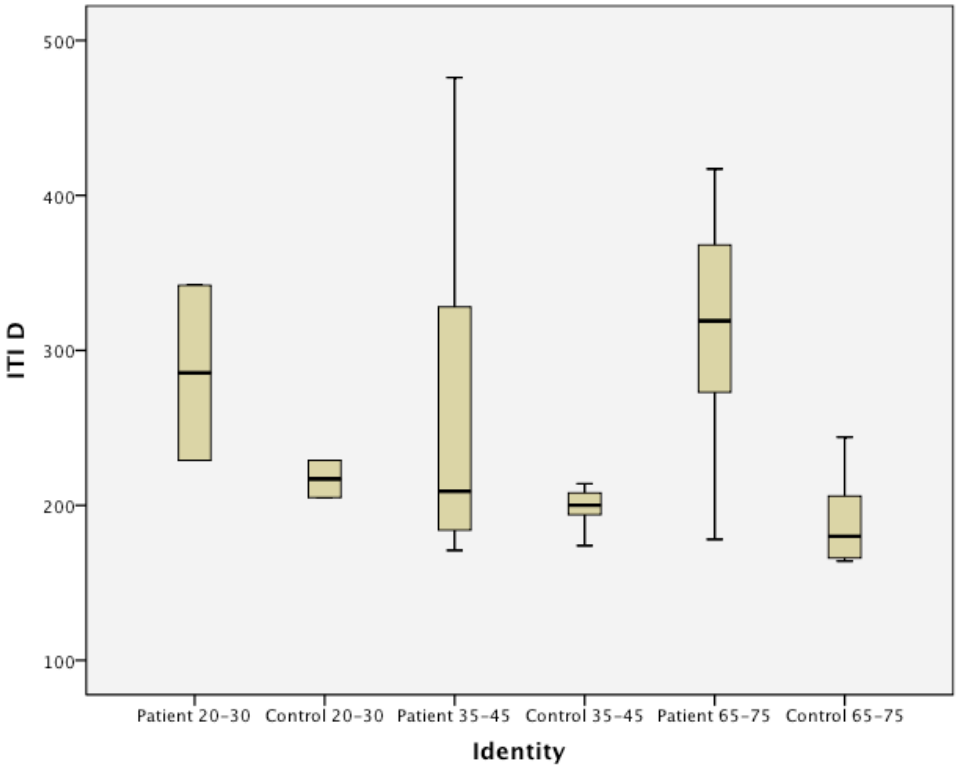
2. ITI D

Inter-tap interval (dominant hand)

ITI D	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	286	217	266	198	312	190
Std Dev	79.9	16.9	102.9	14.5	83.2	30.4
Std Error	56.5	12	34.3	4.8	33.9	12.4
Median	286	217	209	200	319	180
Minimum	229	205	171	174	178	164
Maximum	342	229	476	214	417	244
Range	113	24	305	40	239	80

Table 9.55 Comparison ITI D between HD and controls of the three age groups

ITI D for these groups were non-normal data, and a non-parametric test (NPT), Kruskal- Wallis was used. The tapping rates of HD patients were significantly different from the controls as the p-value was 0.05 on the KW test.



9.29 BW plots showing larger ITI D among patients of the three age groups.

Ranks

	Identity	N	Mean Rank
ITI D	Patient 20-30	2	26.75
	Control 20-30	2	18.75
	Patient 35-45	9	19.11
	Control 35-45	9	13.22
	Patient 65-75	6	25.58
	Control 65-75	6	9.92
	Total	34	

Table 9.56: Ranking of the different groups shows significant difference among the 3 groups of HD vs controls

3. ITI SD

Standard deviation of ITI (dominant hand)

ITI SD D	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	98	17	83.1	36.1	129.2	17.3
Std Dev	54.5	11.2	78.9	27.2	85.2	5.9
Std Error	38.5	7.9	26.3	9.1	34.8	2.44
Median	97.8	126.8	45.8	22.3	116.5	15.5
Minimum	59.2	9.1	13.8	13.9	25.5	13.2
Maximum	136.4	25.1	258.5	92.7	233	29.1
Range	77.1	15.9	245	79	207.4	15.9

Table 9.57 Comparison ITI SD between HD and controls of the three age groups

ITI SD for these groups were non-normal data, and a non-parametric test (NPT), Kruskal-Wallis was used. The tapping rates of HD patients were significantly different from the controls as the p-value was 0.006 on the KW test.

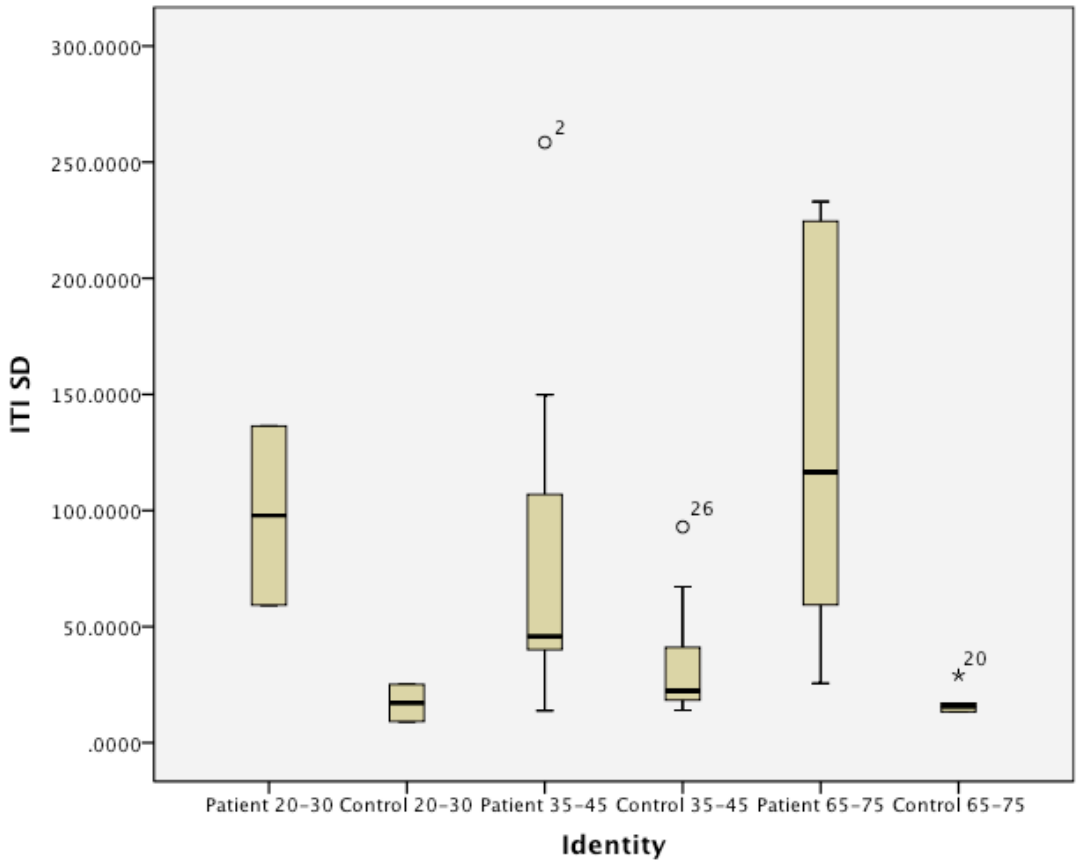


Fig 9.30: BW plots showing larger ITI SD among HD patients of the three groups.

Ranks

	Identity	N	Mean Rank
ITI SD	Patient 20-30	2	26.00
	Control 20-30	2	7.50
	Patient 35-45	9	21.22
	Control 35-45	9	14.89
	Patient 65-75	6	26.50
	Control 65-75	6	7.33
	Total	34	

Table 9.58 Ranking among controls are lower than HD groups.

4. Force D

Tapping force (dominant hand)

Force D	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	9.4	9.6	9.55	9.57	9.58	9.4
Std Dev	0.34	0.007	0.15	0.12	0.25	0.2
Std Error	0.245	0.005	0.05	0.04	0.1	0.09
Median	9.4	9.615	9.6	9.57	9.6	9.6
Minimum	9.16	9.61	9.3	9.3	9.2	9.0
Maximum	9.65	9.61	9.7	9.7	9.8	9.63
Range	0.49	0.01	0.46	0.4	0.6	0.63

Table 9. 59: Comparison Force D between HD and controls of the three age groups

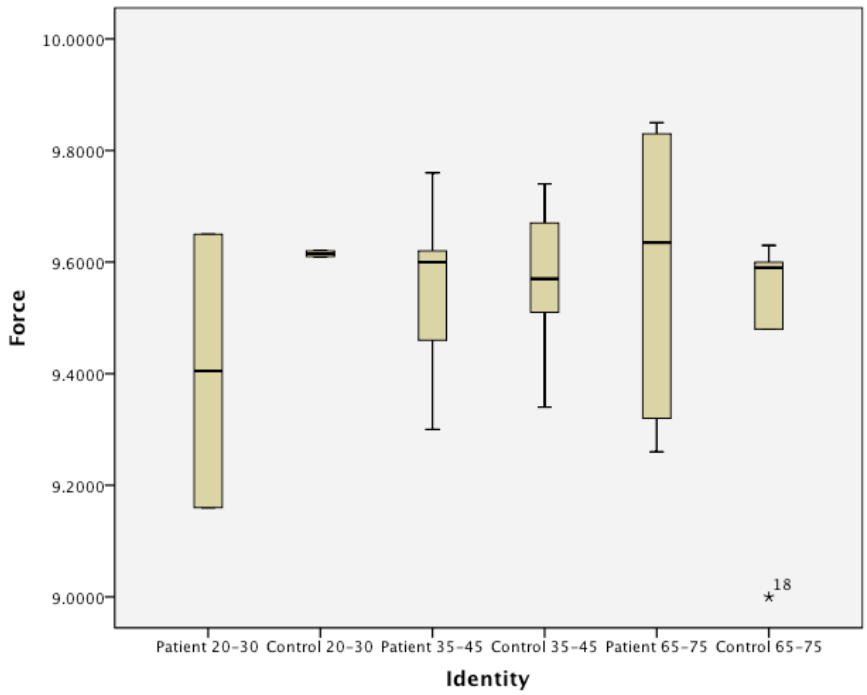


Fig 9.31: BW plots showing comparable force D among the different groups except 20-30s controls.

Force D values for these groups were non-normal data, and a non-parametric test (NPT), Kruskal-Wallis was used. The tapping force of HD patients were not significantly different from the controls as the p-value was 0.922 on the KW test

Ranks

	Identity	N	Mean Rank
Force	Patient 20-30	2	14.00
	Control 20-30	2	22.50
	Patient 35-45	9	17.44
	Control 35-45	9	17.56
	Patient 65-75	6	19.58
	Control 65-75	6	14.92
	Total	34	

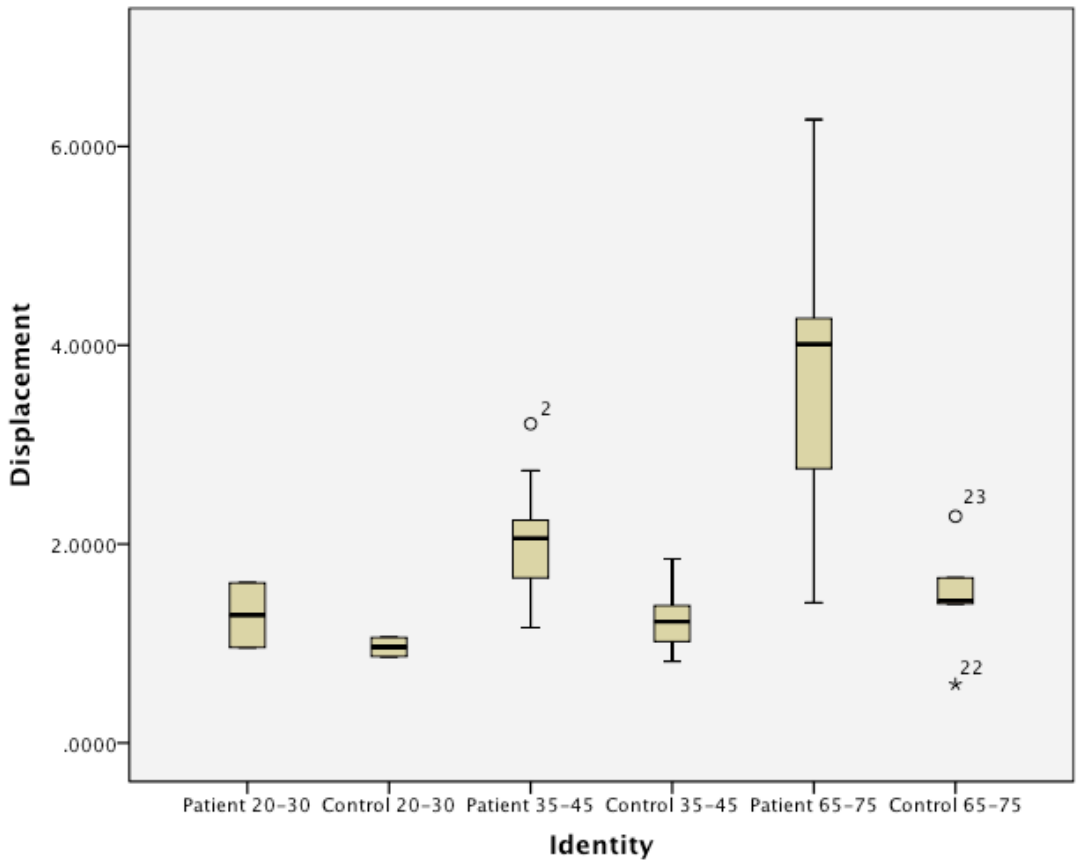
Table 9.60 Ranking did not show a specific pattern among the groups.

5. Displacement D

Displacement from central target (dominant hand)

Displacement	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	1.28	0.96	2.04	1.21	3.78	1.46
Std Dev	0.45	0.13	0.65	0.31	1.62	0.54
Std Error	0.325	0.09	0.21	0.10	0.66	0.22
Median	1.28	0.96	2.06	1.22	4.01	1.43
Minimum	0.96	0.87	1.16	0.82	1.41	0.59
Maximum	1.61	1.06	3.21	1.85	6.27	2.28
Range	0.65	0.19	2.05	1.03	4.86	1.69

Table 9.61 Comparison Displacement D between HD and controls of the three age groups



9.32 BW plots showing larger Displacement D among patients of different HD groups

Displacement D values for these groups were non-normal data, and therefore non-parametric tests (NPT) Kruskal-Wallis was used. The tapping displacement of HD patients were significantly different from the controls as the p-value was 0.003 on the KW test.

Ranks

	Identity	N	Mean Rank
Displacement	Patient 20-30	2	12.00
	Control 20-30	2	5.25
	Patient 35-45	9	21.94
	Control 35-45	9	10.33
	Patient 65-75	6	29.00
	Control 65-75	6	16.00
	Total	34	

Table 9.62 Ranking shows lower values of Displacement D among controls of all groups.

2. Speeded or fast – Double target

1. Taps R D – Number of taps on the R target with the dominant hand

Taps R D	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	29	45	27	40	25	36
Std Dev	9.89	19.8	7.33	8.96	8.32	6.31
Std Error	7.00	14	2.44	2.99	3.4	2.6
Median	29	45	27	38	22	34
Minimum	22	31	17	30	17	31
Maximum	36	59	38	57	36	47
Range	14	28	21	27	19	16

Table 9.63 Comparison Taps R D between HD and controls of the three age groups

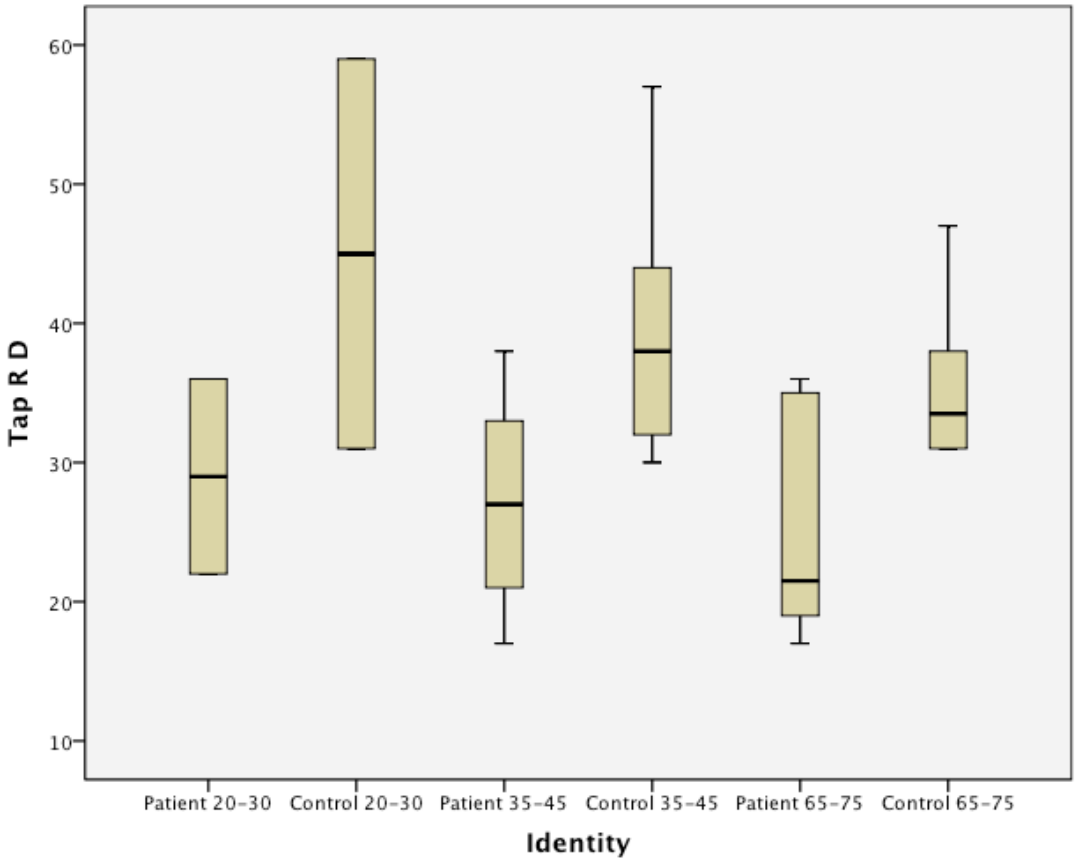


Fig 9.33 BW plots showing lower Taps R D among HD patients of all groups.

Taps R D values for these groups were non normal data, and a non-parametric test (NPT), Kruskal- Wallis was used. The tapping rates of HD patients were significantly different from the controls as the p-value was 0.04 on the KW test.

Ranks

	Identity	N	Mean Rank
Tap R D	Patient 20-30	2	15.75
	Control 20-30	2	24.50
	Patient 35-45	9	12.00
	Control 35-45	9	24.06
	Patient 65-75	6	10.50
	Control 65-75	6	21.17
	Total	34	

Table 9.64 Ranking shows higher Taps R D values among all control groups

2. Taps L D – number of taps on the left target with the dominant hand.

Taps L D	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	30	46	27	40	25	35
Std Dev	10.6	19.1	6.81	8.96	8.21	5.4
Std Error	7.5	13.5	2.3	2.9	3.35	2.2
Median	29.5	45	27	37	22	34
Minimum	22	32	18	30	17	31
Maximum	37	59	37	57	35	45
Range	15	27	19	27	18	14

Table 9.65 Comparison Taps L D between HD and controls of the three age groups

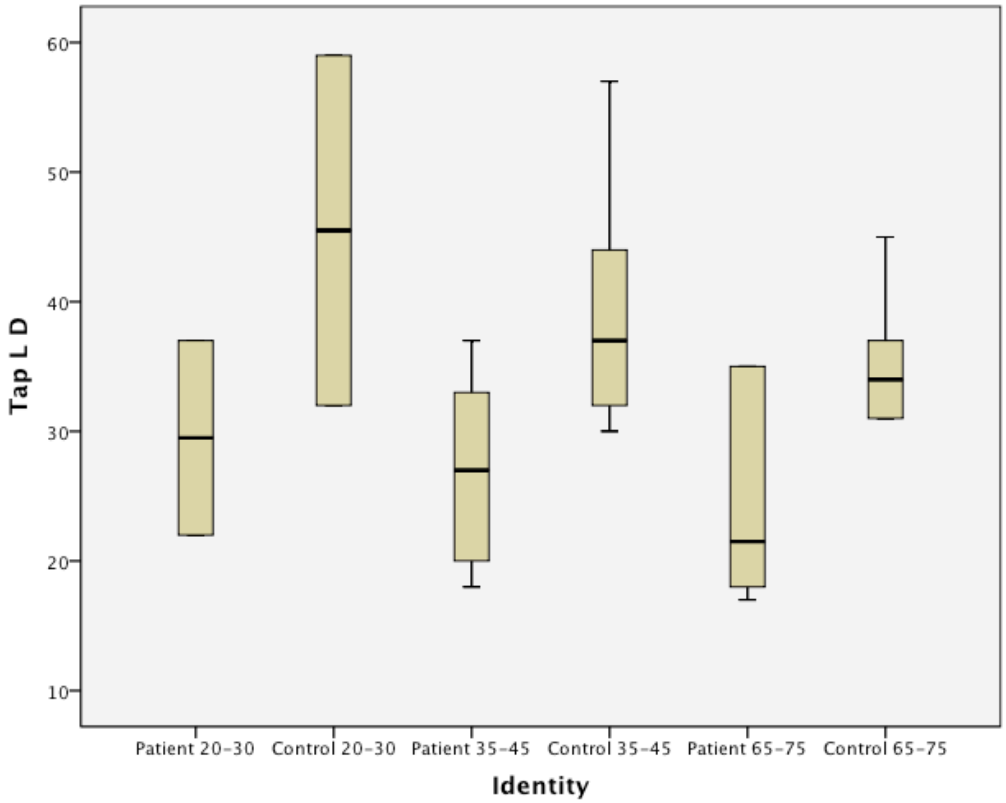


Fig 9.34: BW plots showing lower Taps L D among all groups of HD

Taps L D values for these groups were non-normal data, and a non-parametric test (NPT), Kruskal- Wallis was used. The tapping rates of HD patients were significantly different from the controls as the p-value was 0.03 on the KW test.

Ranks

	Identity	N	Mean Rank
Tap L D	Patient 20-30	2	17.00
	Control 20-30	2	25.25
	Patient 35-45	9	12.11
	Control 35-45	9	24.22
	Patient 65-75	6	10.00
	Control 65-75	6	20.58
	Total	34	

Table 9.66 Ranking shows lower values of Taps RD among all HD groups.

3. ITI D – Inter-tap-interval of taps on alternate targets with the dominant hand.

ITI D	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	531.5	351.5	570.3	379.4	621.1	415.3
Std Dev	177.8	150.6	159.8	76.7	174.7	58.9
Std Error	121.5	106.5	53.28	25.6	71.3	24.06
Median	531.5	351.5	543	386	656.5	430.5
Minimum	410	245	389	255	412	316
Maximum	653	458	832	483	839	471
Range	243	213	443	228	427	155

Table 9.67 Comparison ITI D between HD and controls of the three age groups

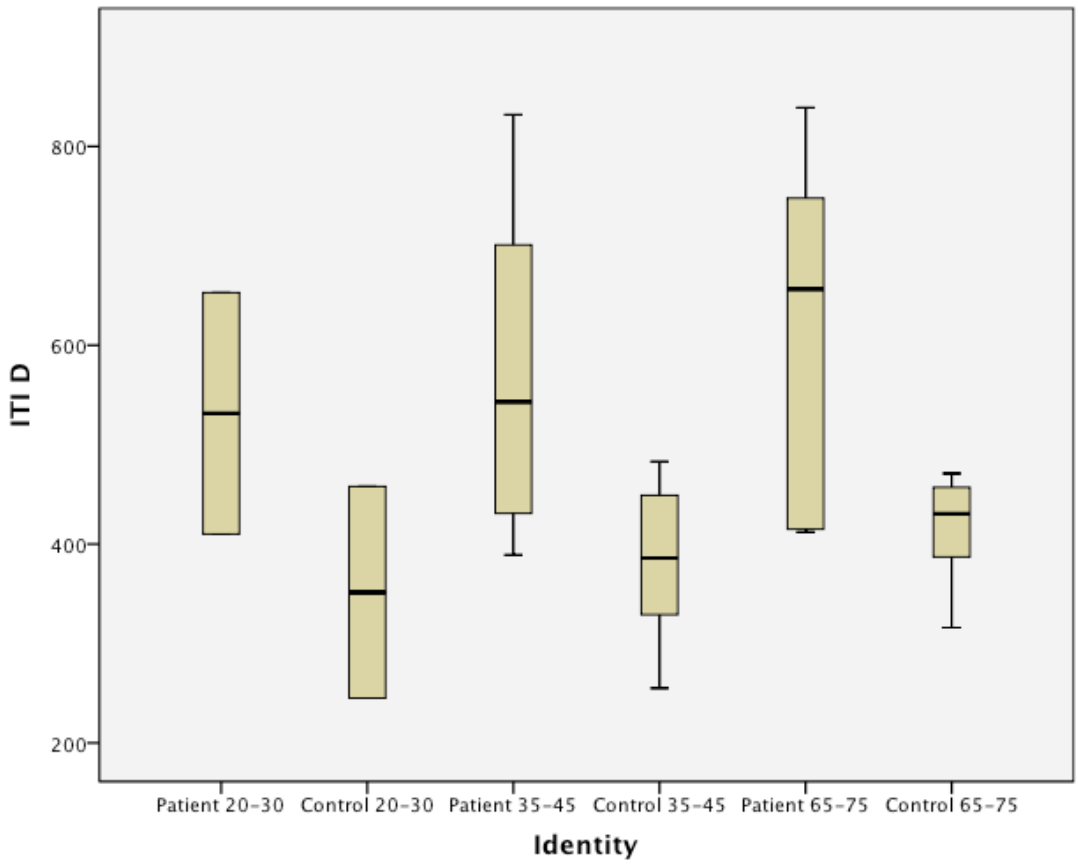


Fig 9. 35 BW plots showing higher ITI D among all groups of HD.

ITI D values for these groups were non normal data, and a non-parametric test (NPT), Kruskal- Wallis was used. The tapping rates of HD patients were significantly different from the controls as the p-value was 0.028 on the KW test.

Ranks

	Identity	N	Mean Rank
ITI D	Patient 20-30	2	20.00
	Control 20-30	2	11.00
	Patient 35-45	9	23.22
	Control 35-45	9	10.33
	Patient 65-75	6	24.67
	Control 65-75	6	13.83
	Total	34	

Table 9.68 Ranking shows higher values of ITI D among all HD patient groups.

4. ITI SD

Standard deviation of ITI SD (dominant hand)

ITI SD	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	87.6	33.4	114.4	39.5	208.2	35.3
Std Dev	12.5	12.72	65.12	10.9	147.42	11.53
Std Error	8.85	9	21.71	3.66	60.18	4.71
Median	87.6	33.45	85.6	35.8	163.5	32.67
Minimum	78.7	24.45	31.2	25.4	51	22.34
Maximum	96.4	42.44	222.2	57.12	422.9	56.2
Range	17.7	17.99	191	31.68	371.9	33.9

Table 9.69 Comparison ITI SD between HD and controls of the three age groups

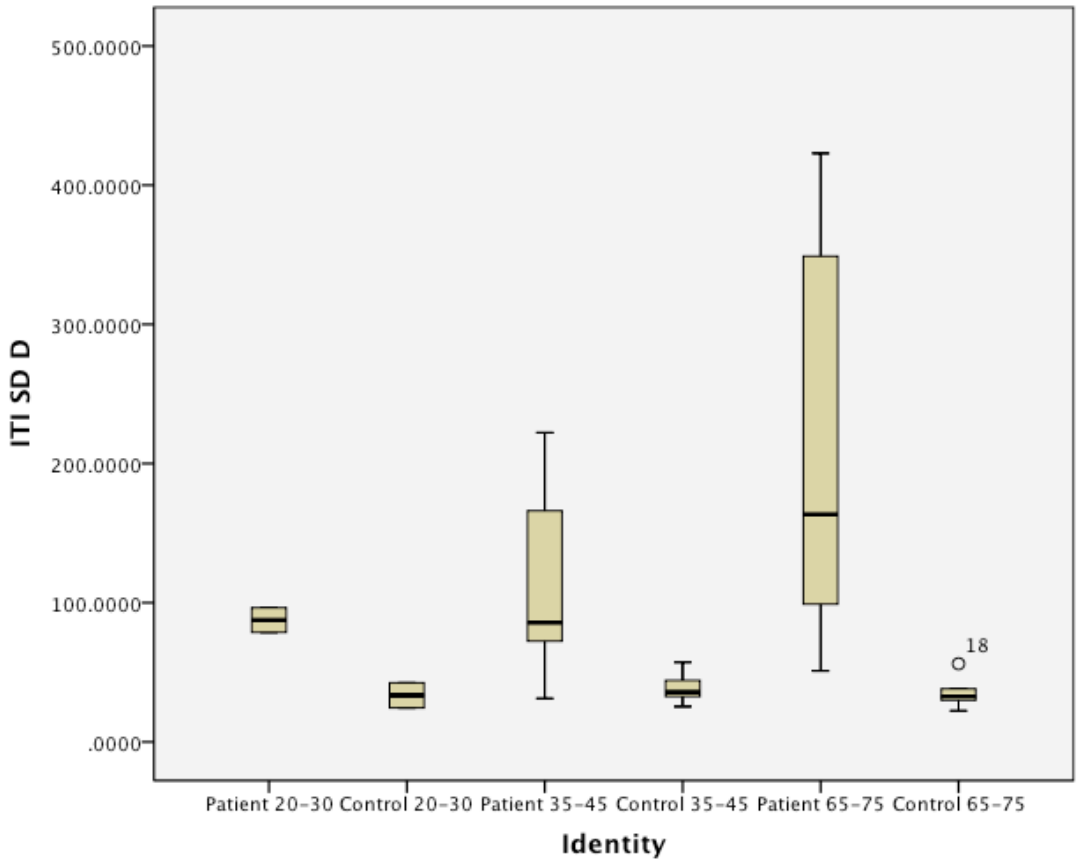


Fig 9.36 BW plots showing higher ITI SD among all HD patient groups.

ITI SD values for these groups were non-normal data and a non-parametric test (NPT), Kruskal-Wallis was used. The tapping rates of HD patients were significantly different from the controls as the p-value was 0.001 on the KW test.

Ranks

	Identity	N	Mean Rank
ITI SD D	Patient 20-30	2	24.00
	Control 20-30	2	8.00
	Patient 35-45	9	23.56
	Control 35-45	9	11.00
	Patient 65-75	6	28.00
	Control 65-75	6	8.67
	Total	34	

Table 9.70: Ranking shows ITI SD of all HD patient groups are higher.

5. Displacement R D

Displacement from the right target (dominant hand)

Displacement R D	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	2.04	3.47	3.71	3.54	5.1	3.5
Std Dev	0.67	2.55	1.33	1.14	2.57	1.17
Std Error	0.48	1.8	0.44	0.38	1.05	0.48
Median	2.04	3.47	3.22	3.38	4.42	3.32
Minimum	1.56	1.67	2.22	2.02	2.63	2.09
Maximum	2.52	5.28	6.73	5.72	9.26	5.43
Range	0.96	3.61	4.48	3.7	6.63	3.34

Table 9.71 Comparison Displacement R D between HD and controls of the three age groups

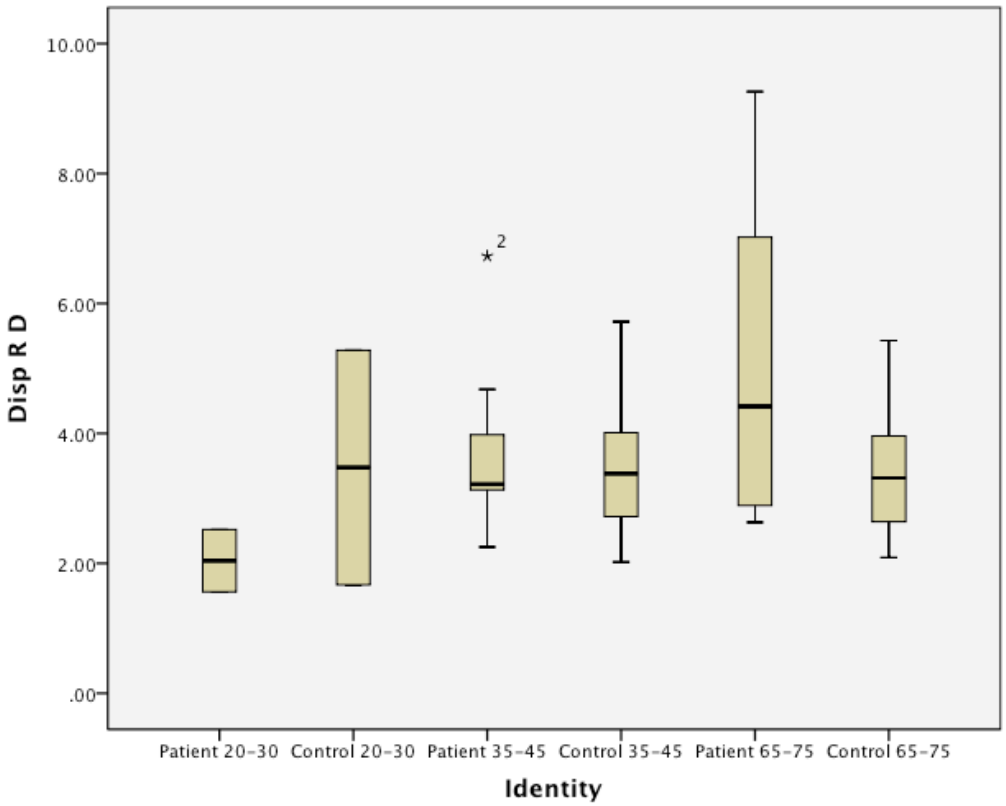


Fig 9.37 BW plots comparable Displacement R D values though the HD patient values appear minimally reduced

Displacement R D values for these groups were non-normal data, and a non-parametric test (NPT), Kruskal-Wallis was used. The tapping rates of HD patients were not significantly different from the controls as the p-value was 0.32 on the KW test.

Ranks

	Identity	N	Mean Rank
Force R D	Patient 20-30	2	14.75
	Control 20-30	2	31.50
	Patient 35-45	9	12.61
	Control 35-45	9	21.06
	Patient 65-75	6	14.50
	Control 65-75	6	18.75
	Total	34	

Table 9.72 Ranking does not show a pattern among groups.

6. Displacement L D

Displacement from the left target (Dominant hand)

Displacement L D	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	3.03	2.71	3.28	3.03	3.46	3.19
Std Dev	1	1.32	0.72	0.79	1.85	1.16
Std Error	0.71	0.94	0.24	0.26	0.76	0.47
Median	3.03	2.71	3.57	3.01	3.24	3.00
Minimum	2.32	1.77	2.23	1.74	1.34	1.89
Maximum	3.74	3.64	4.42	4.4	6.7	5.31
Range	1.42	1.87	2.19	2.66	5.36	3.42

Table 9.73 Comparison Displacement L D between HD and controls of the three age groups

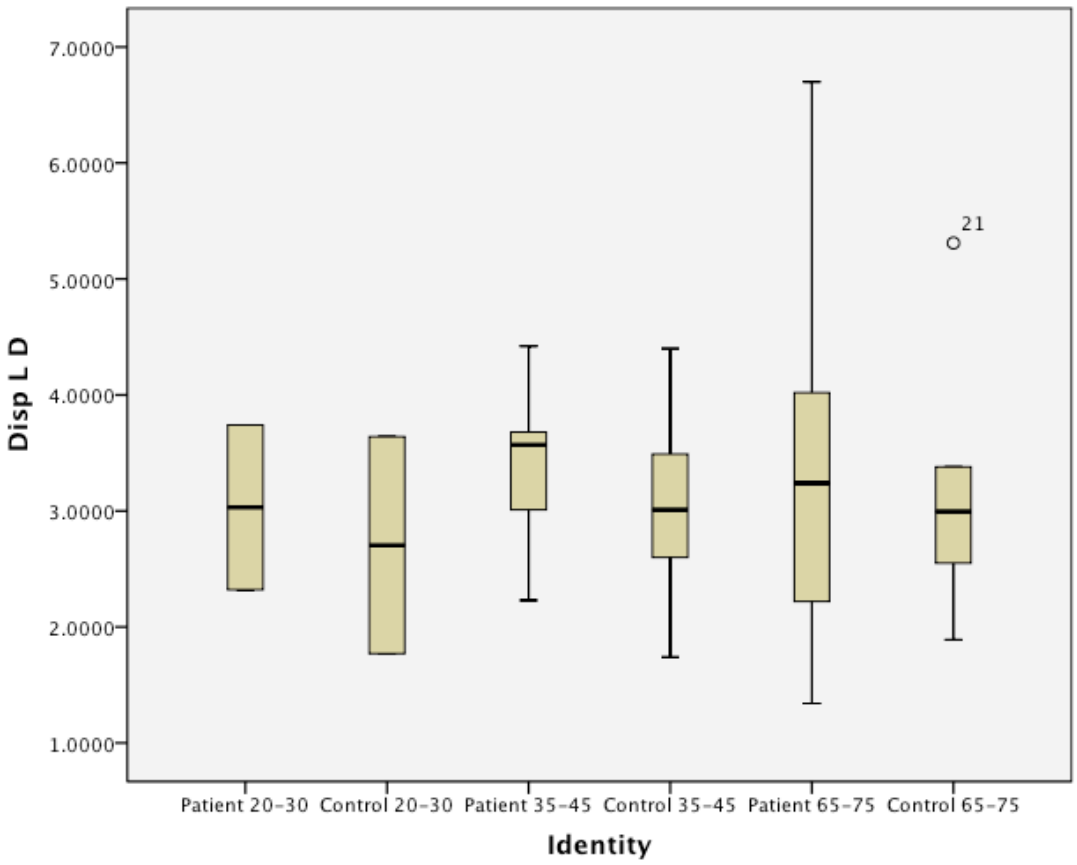


Fig 9.38 BW plots show comparable Displacement L D among all groups.

Displacement L D values for these groups were non-normal data, and a non-parametric test (NPT), Kruskal- Wallis was used. The tapping rates of HD patients were not significantly different from the controls as the p-value was 0.945 on the KW test.

Ranks

	Identity	N	Mean Rank
Disp L D	Patient 20-30	2	19.00
	Control 20-30	2	14.50
	Patient 35-45	9	20.11
	Control 35-45	9	15.89
	Patient 65-75	6	17.83
	Control 65-75	6	16.17
	Total	34	

Table 9.74 Ranking does not show a pattern among groups

3. Simple Reaction Time task

1. RT4 D - Reaction time with the dominant hand

RT4 D	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	767.5	513.5	695.4	503.9	887.3	606
Std Dev	226.9	58.69	129.4	25.77	316.97	84.25
Std Error	160.5	41.5	43.2	8.59	129.4	34.4
Median	767.5	513.5	727	504	848	619
Minimum	607	472	509	472	520	504
Maximum	928	555	907	557	1385	699
Range	321	83	398	85	865	182

Table 9.75 Comparison of RT4 D between HD and controls of the three age groups.

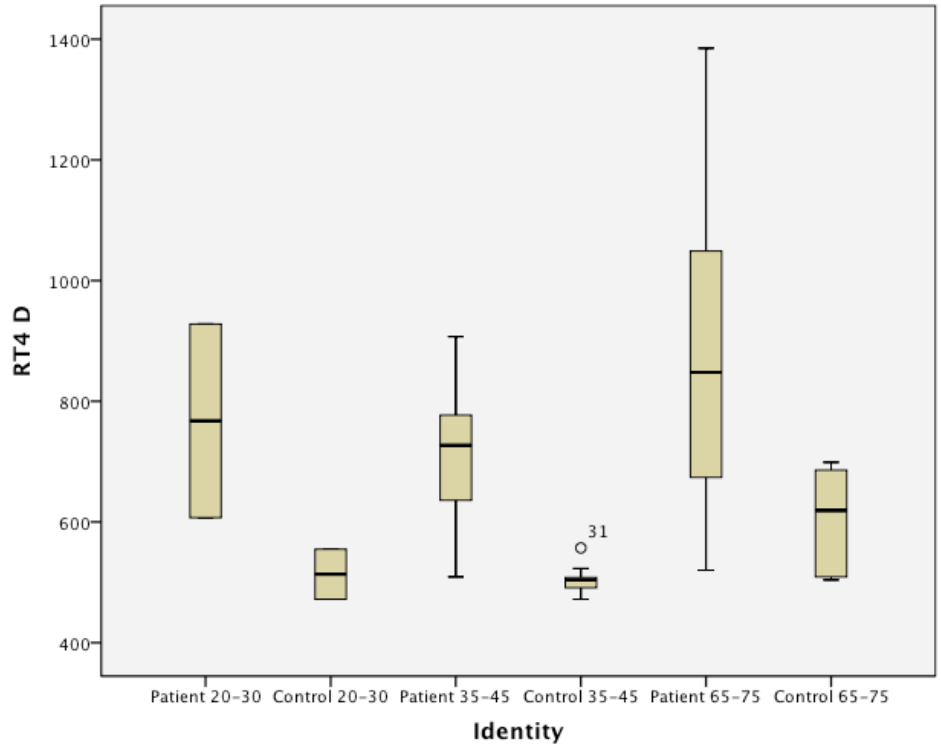


Fig 9.39 BW plots show higher RT4 values among all HD patients

Reaction time values for these groups were non-normal data, and a non-parametric test (NPT), Kruskal-Wallis was used. The tapping rates of HD patients were significantly different from the controls as the p-value was 0.002 on the KW test.

Ranks

	Identity	N	Mean Rank
RT4 D	Patient 20-30	2	24.25
	Control 20-30	2	8.25
	Patient 35-45	9	22.72
	Control 35-45	9	7.44
	Patient 65-75	6	26.17
	Control 65-75	6	16.92
	Total	34	

Table 9.76 Ranking shows all groups of controls to have lower RT4 D than all groups of HD

2. RT4 SD – Standard deviation of Reaction time with the dominant hand in the pro-tap task.

RT4 SD	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	118.8	37.6	110.8	48.3	304.34	68.09
Std Dev	70.29	9.28	43.9	16.2	252.68	33.29
Std Error	49.7	6.57	14.6	5.4	103.16	13.59
Median	118.8	37.64	94.8	49.6	229	52.38
Minimum	69.1	31.07	39.5	28.2	72.14	41.28
Maximum	168.5	44.2	165.2	75	792.9	126.6
Range	99.4	13.13	125.7	46.83	720.76	85.32

Table 9.77 Comparison of RT4 SD between HD and controls of the three age groups

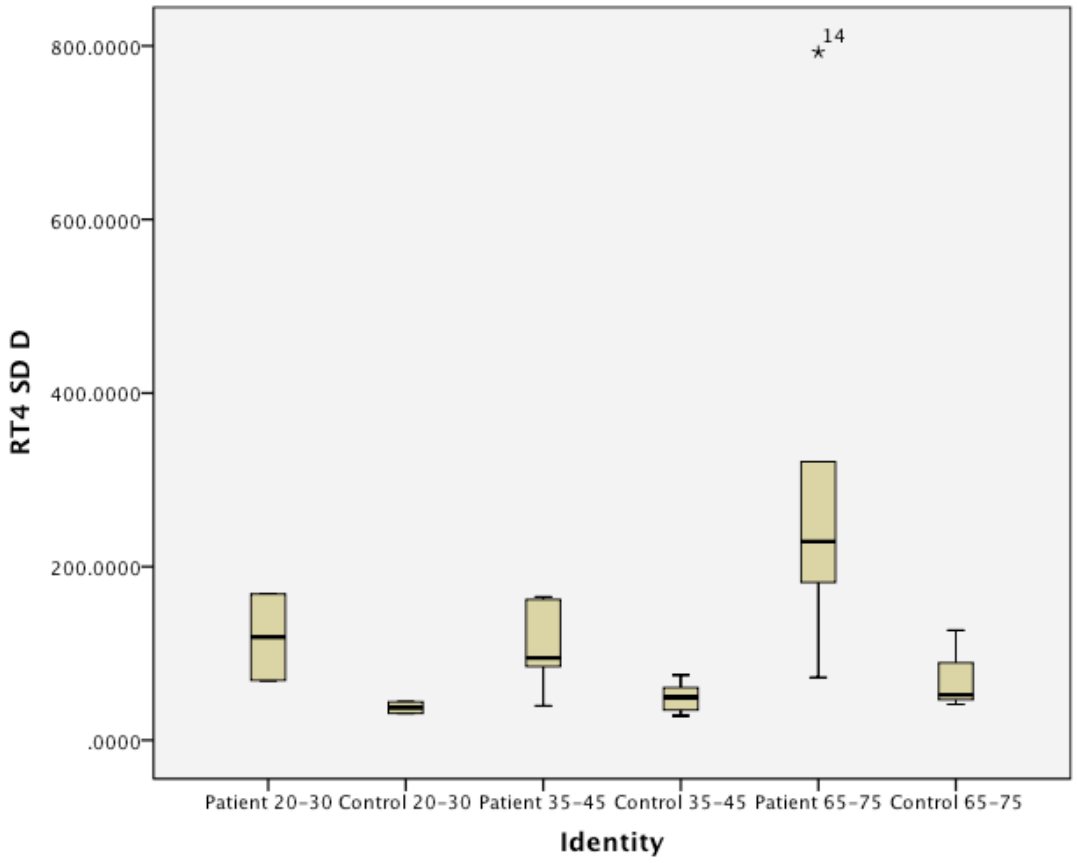


Fig 9.39 BW plots of RT SD show wider ranges and larger values among all groups of patients

Reaction time values for these groups were non-normal data and therefore a non-parametric test (NPT), Kruskal- Wallis was used. The reaction times of HD patients were significantly different from the controls as the p-value was 0.001 on the KW test.

Ranks

	Identity	N	Mean Rank
RT4 SD D	Patient 20-30	2	22.50
	Control 20-30	2	5.00
	Patient 35-45	9	21.67
	Control 35-45	9	9.22
	Patient 65-75	6	29.50
	Control 65-75	6	14.17
	Total	34	

Table 9.78 Ranking shows lower RT4 SD values among groups of all controls.

4. Choice Reaction time or Anti-tap task

1. RT5 D - Reaction time with the dominant hand in the anti-tap task

RT5 D	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	823	510.5	955.6	595.4	1207.7	760.2
Std Dev	196.6	0.70	315.28	75.8	381.4	107.24
Std Error	139	0.5	105.1	25.2	155.7	43.78
Median	823	510.5	957	596	1215.5	800
Minimum	684	510	539	516	571	610
Maximum	962	511	1538	694	1714	877
Range	278	1	999	178	1143	267

Table 9.79: Comparison of RT5 D between HD and controls of the three age groups

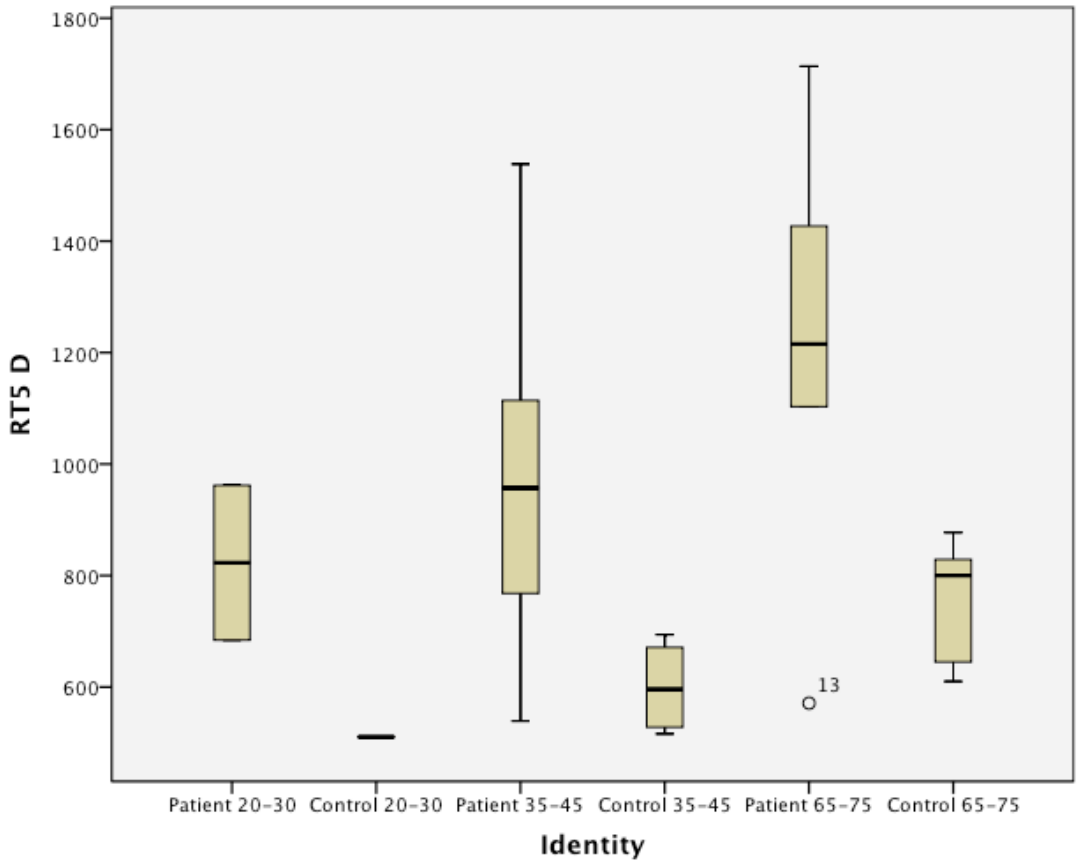


Fig 9.40 BW plots of show larger RT5 D values among all HD patients compared to controls of all age groups

Reaction time values for these groups were non-normal data, and a non-parametric test (NPT), Kruskal-Wallis was used. The reaction times of HD patients were significantly different from the controls as the p-value was 0.003 on the KW test.

Ranks

	Identity	N	Mean Rank
RT5 D	Patient 20-30	2	20.00
	Control 20-30	2	1.50
	Patient 35-45	9	21.89
	Control 35-45	9	9.56
	Patient 65-75	6	26.83
	Control 65-75	6	18.00
	Total	34	

Table 9. 80 Ranking of all age groups of HD and controls shows lower RT5 D values among controls

2. RT5 SD – Standard deviation of reaction time in the anti-tap task (dominant hand)

RT5 SD	20-30 Pt	20-30 controls	35-45 Pt	35-45 controls	65-75 Pt	65-75 controls
Mean	121.5	47.4	279.6	85.7	561.2	107.6
Std Dev	80.5	16.7	247	38.9	386.1	30.2
Std Error	56.9	11.8	82.3	12.9	156.7	12.33
Median	121.5	47.44	188.1	78.7	545	115.6
Minimum	64.5	35.6	73.1	41.5	87.2	59.3
Maximum	178.4	59.2	872.5	170.8	1026	137.9
Range	113.9	23.6	799.4	129.2	938	78.6

Table 9.81 Comparison of RT5 SD between HD and controls of the three age groups

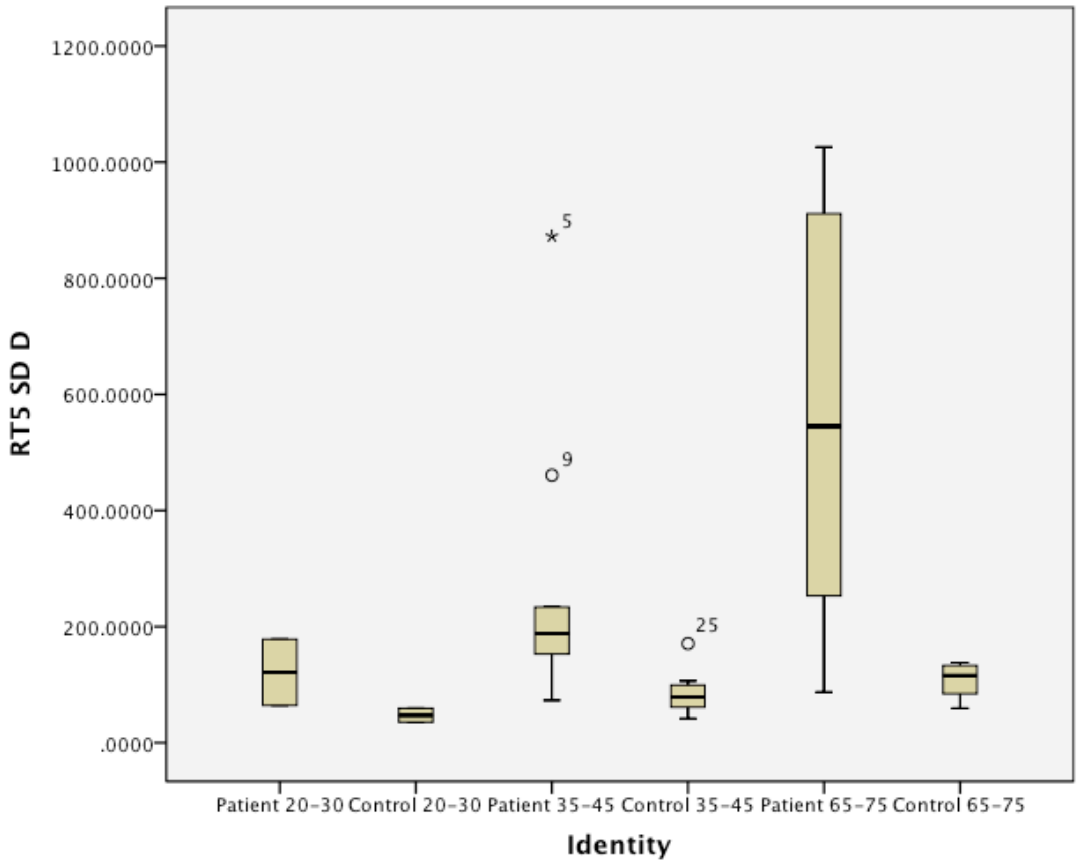


Fig 9.41 BW plots show larger RT5 SD among all groups of HD compared to all age groups of controls

Reaction time values for these groups were non-normal data, and a non-parametric test (NPT), Kruskal- Wallis was used. The reaction times of HD patients were significantly different from the controls as the p-value was 0.002 on the KW test.

Ranks

	Identity	N	Mean Rank
RT5 SD D	Patient 20-30	2	15.00
	Control 20-30	2	2.50
	Patient 35-45	9	23.44
	Control 35-45	9	10.44
	Patient 65-75	6	27.83
	Control 65-75	6	14.67
	Total	34	

Table 9. 82 Ranking shows higher RT5 SD D among all groups of HD patients.

Chapter 10

Discussion

10.1 Cross sectional study of different age groups

The primary purpose of the cross sectional study was to obtain baseline values for the various tapping measures, and secondarily, to look for any variation in tapping parameters and reaction times among the different age groups.

Only results obtained from the dominant hand were used, as there were no significant differences in their performance both in the pilot study as well as in the final experiment.

When normal data was available, t-tests and ANOVA were performed. However, since the majority of the data was non-normal due to small sizes, non-parametric tests suited to the variables were performed.

1. Single finger tapping

Tapping rate was significantly lower in the 65 -80s group compared to the 20-30s group. Although, a graded decrease in tapping was not anticipated, the tapping rates did appear lower among the 35-45 and the 65-80s groups than the 20-30s in a graded manner. No other studies documenting an age difference in these specific tapping tasks were found in my literature search. The 65-80s group showed a wider range in tapping rates, though even the best did not outperform the two other groups.

Inter-tap-interval (ITI) and inter-tap-interval standard deviation, which can be referred to as variability, did not show any significant difference between these three groups. ITI standard deviation may be an indicator of motor rhythmic being generated, though it needs to be further studied.

Force did not show any significant differences between any of the groups. Force documented by this device was derived by measuring changes in the 'g' since the device was equipped with an accelerator. The device measured force with respect to gravity and therefore has a baseline reference of 9.8 m/s2. In the tapping tasks, force was taken as a point measure, though an ideal measurement of force would have been a continuous one, showing changes in acceleration before, during and after the tap. It was beyond the scope of my study to develop

a separate program for force, and hence only point forces were documented. However, further work in this regard may yield valuable information about the patterns of force in different age groups.

Displacement was calculated as the deviation from the original target. The device has a screen resolution of 1024 x 600. Baselines values were obtained from the various age groups, which provided a reference to the real deviation from the target on the screen. 20-30s and 35-45s were both significantly different from the 65-80s group. This was largely because the 20-30s and 35-45s functioned as a single group and did not appear to have any problem with tapping nearer to the target. This could be an indicator of age related motor decline, and documenting this baseline would serve as a useful reference when comparing controls and other subjects, and delineate age related and disease related decline in motor performance.

2. Double target tapping

Taps R and taps L were the tapping rates (counts) on the two respective targets. Both measures did not show any significant difference between the three age groups. The test was short, albeit tapping between the two targets without moving the wrist was an effort which even the 20-30s groups, had to contend with. This may have led to a dilution of the difference in tapping rates, and may have been a contributor to the near similar performance by all three groups.

Moving the targets closer was an option, which was not undertaken as the distance between the targets studied is the same as that used in other tapping devices such as the Ober (Antoniades et al, 2012, 2009). The Ober device has documented differences in PD subjects and controls with this distance, however there are no studies involving different age groups. Larger group sizes, and variation of distances would be an option in future studies to understand if the parameter's ability to differentiate between groups differs with a change in distance.

Inter-tap-interval was significantly different between the 20-30s group and the 65-80 groups. The effect of difference in the tapping rates may have diminished due to the short amount of time dedicated to each target (15 seconds), which may not have been adequate to segregate the tapping rate performance per target. However, the inter-tap-interval was the time taken to tap between the two targets was calculated during the whole tapping duration (30s), which is likely to be the cause for the inter-tap-interval failing to identify a difference in performance in the two groups.

Force was measured but was not described in the results section as its values were very similar to the first test and did not yield any significant results.

3. Metronome task

No significant differences were obtained in the tapping patterns of the different age groups with respect to tapping to the metronome. Some 20-30s tapped much faster than the metronome in the no-cue phase, the effect of which was not seen when the results were looked as a group.

4. Pro-tap task (Simple reaction time)

The reaction time in the pro-tap task was a simple reaction time test, which showed a significant difference across all groups. A pattern similar to the previous tests emerged, where in 20-30s and 35-45 yrs groups had significantly shorter reaction times than the 65-80s group. However, the 20s-30s and 35-45s groups did not show a significant difference in their reaction times. Similarly standard deviations of reaction times showed the same pattern, denoting variability in reaction times was higher in the older group, i.e, 65-80s group which could possibly also be an indicator of motor decline.

5. Anti-tap task (Choice reaction time)

A similar pattern to the pro-tap task was observed between the three different groups. Reaction times in the anti-tap task in the older group (65-80s) were longer than both the other two groups; the standard deviations were also much larger. The shortest reaction time in the 65-80s was longer than the longest

reaction time in the other 2 groups. The difference in reaction time, though not the same as reaction times which were impaired due to a decrease in voluntary inhibition, were longer than the other and were significantly different, for which various causes maybe attributed.

The goal was to derive baseline values for all these measures, which served as a reference in the following two studies. A previous pilot study was performed, and the tapping rates, inter-tap-intervals, reaction times and displacements matched as those with the pilot group. A larger sample size was able to show a difference in inter-tap-variability, and standard deviation of reaction times.

10.2 Case control study of PD patients and controls.

1. Finger tapping – Single target

A straightforward comparison between age-matched PD subjects and controls showed a significant difference in tapping rates (count). The effect of aging is clearly separated in this simplified motor test, and an objective score of the tapping rate is obtained through the device.

Inter-tap-interval and inter-tap variability were not significantly different between the PD subjects and controls, which was a pattern also noted in the pilot study. Understanding this pattern requires a rethink on how inter-tap-interval is calculated, as inter-tap interval is calculated as the time between taps. A difference in inter-tap-interval should also reflect a difference in the tapping rate, which perhaps suggests a pattern (or lack of) in the manner of tapping among the PD patients. A lingering tap with a prolonged lowering onto the tapping surface and prolonged lifting off maybe a contributor to this effect. This effect can be studied further, by measuring acceleration throughout the tap, i.e, before, after and during the tap, may give us more information concerning the mechanism of tapping by a PD patient.

Force as described earlier did not show any significant difference as the force measured is a point force, and further studies with continuous tracking of the acceleration/deceleration of the finger may prove of greater value.

Displacement was significantly higher in PD patients than controls, and the range of the displacement was also higher, albeit even the lowest displacement value in a PD patient was higher than the control with the highest value. Thus, displacement through the tapping test appears to be an objective measure of detecting differences in the accuracy of tapping.

2. Finger tapping- double target

Tapping rates in the PD patients were much lower than controls in both tapping rates measures of the two targets, similar to the tapping pattern in the first task with a single target.

Inter-tap-intervals and inter-tap- variability were both significantly higher in PD patients unlike the test with the single target. The double target tapping involves movement between two targets, and therefore includes a movement time, and time to plan a straight horizontal movement between the two targets to ensure accuracy. Few PD patients tapped outside the target, and those who tapped in took longer, which could have led to the longer inter-tap-intervals and variability.

Force on the two targets did not show a significant difference, as anticipated. Displacement R and L of the two targets did not show a significant difference between the PD patients and controls.

3. Pro-tap time (Simple reaction time)

Reaction times and their standard deviation were significantly higher in PD patients versus controls. Previous studies (refer to table 5.1) in PD patients showed longer reaction times. The studies though different, mainly had similar results as in the reaction time, although the variability of the reaction time was mixed. The ability to react and plan the same response 20 times in one task appears to be impaired in PD patients. This could be explained by a decrease in the ability to plan and execute a response repeatedly a problem often seen clinically in the alternating hand test.

Another useful aspect of the test is an automated method of performing the tests and deriving results for simple and choice reaction times.

4. Anti-tap time

Anti-tap reaction times were longer in PD patients, and the standard deviation of anti-tap reaction times (variability) was even longer in the PD patients in comparison with the pro-tap task.

Among the PD patients there appears to be a greater variation in the ability to inhibit the action and the choice of the appropriate response. The anti-tap task appears to have an edge in being able to detect a significant difference between PD subjects and controls due to its larger values.

10.3 Case-control study of HD patients and controls

1. Finger tapping – Single finger

The HD patients were divided into three groups of MHD patients. The patients were divided by age into the 20-30s, 35-45 and 65-75 year old groups. All controls were age matched.

Comparisons for all measures were made across the group and between individual groups.

Tapping rates though slightly lower than controls among HD patients, were not significantly different. As known from the clinical features of HD patients, the subjects did not appear to be affected in *performing* a simple motor task, but appeared to be affected in terms of accuracy. Tapping rates just measure the ability of the subject (or control) to tap on the specified target within the specified amount of time, which did not seem to be a deficient in HD patients. Despite the dyskinesia the subjects were able to tap, albeit not always on the specified central sub-target present within the target.

Inter-tap intervals and their variability were significantly higher in HD patients, as expected. Dyskinesia would be more likely to affect one's ability to tap in a sustained, regular manner, which was the case with our data.

Force did not show any difference between HD and controls.

Displacement values of HD patients were higher than expected. All groups of HD patients showed higher values than their age matched controls. Displacement is also a measure, which could be a potential indicator and objective measure of dyskinesia as it measures the degree of inaccuracy of the tap, which was expected in the case of HD patients.

2. Finger tapping – Double target

Tapping rates on double targets, ie, Taps R and Taps L were both significantly lower in HD patients. During the course of the study, the finger-tapping task was noted to be the most difficult for HD patients. During the pilot study, this test provided similar results, though it had a test time of 45 seconds. However, as I noticed most HD subjects struggled with this test, I decreased the duration of the test to 30 seconds, and have found similar results. Future testing could include a decrease in the time of this test to the point of appropriate sensitivity, as well as maximum comfort for the subject.

The second tapping task as described earlier, is more difficult to perform because of the horizontal movement and distance between the two targets. The difficulty level maybe further increased in a HD patient, due to dystonia.

Inter-tap-interval and inter-tap variability were also found to have higher values in HD subjects similar to one other study using the OBER in HD patients. Inter-tap variability is an additional difference in our study, which further establishes the difficulty in maintaining a consistent rhythm in HD.

Displacement values were not significantly different between HD patients and controls, similar to the pattern seen in PD patients. The difficulty level of the test may be diluting the effect seen in displacement, as displacement was higher in the single tap test, which was easier to perform.

3. Pro-tap task (Simple reaction time)

The pro-tap task reaction times and variability were higher in HD subjects than controls. It is in accordance with previous studies involving simple reaction time and saccades, which show longer reaction times in HD patients. The controls had small standard deviations compared to the HD subjects, though none of the HD subjects had a lower reaction time than the controls.

4. Anti-tap task (Simple reaction time)

The anti-tap task reaction times and its standard deviations were similar to the pro tap task and were significantly higher in the HD patients. The values for the anti-tap reaction times were much higher than the controls, in comparison to the pro-tap reaction times. Though it does not necessarily imply a difference in voluntary inhibition, the variability of anti-tap reaction time was higher than the variability of the pro-tap variability, which points in that direction.

Limitations of the study

Device

The ability to the device was accepted as a computerised tablet and no further tests were made to ascertain the performance of the system in registering taps or touch in comparison to other tested hand tapping devices. The tablet was tested only against the Ober (another standardised tapping device) and the tapping values were comparable. However, since other tapping tests and reaction time tasks are being studied, there is a need to ensure that the touch, temporal resolution and tap performance of the system are validated through other measures to enable a confirmation of the 'true' value both in terms of real time and consistency of values.

Sample size

The sample size for the sub–groups of the HD patients were too small to be classified as separate groups. Though included in the study, a larger sample size was necessary to have an accurate depiction of the true values in those sub-groups.

Statistical parameters

The individual values obtained from the device were analyzed by an in built program, which provided a mean value for each tapping parameter. This mean value was obtained with an assumption that the data obtained was normal in distribution. Either ascertaining whether the individual values were normal or obtaining median values would have given us an accurate picture of the values we were looking for.

The ITI and ITI SD were analyzed independent of each other, however statistically the two variables being invariably dependent on each had to be looked at in conjunction with each other, and in this context coefficient of variation would have been a less ambiguous variable.

10.4 Consolidated discussion & Conclusion

The main objective of our study was to investigate whether finger tapping could be a useful clinical biomarker in HD and PD. We used various tests to identify a pattern of finger tapping performance among different age groups, as well as between HD, PD patients and controls.

This helped us establish a baseline for the appropriate age group for the purpose of the study and to compare PD and HD patients with the controls.

The use of this device has helped us unify the study of various tapping measures and reaction times to be studied through one portal for PD, HD and controls. It's consistent values to previous studies (Tables 5.1 & 5.2), and additional variables discussed earlier help us objectify the difference in PD, HD subjects and controls, which takes us one step closer to establishing finger tapping as a biomarker. It has provided us with solid differences in all tapping tasks between PD, HD and controls, reiterating previous studies and providing us with new measures as well.

In conclusion, motor performance in the form of finger tapping tasks is a viable clinical biomarker in PD and HD.

10.5 Improvements to the device and protocol

Point forces were measured thorough the task. A program to measure continuous force during the entire duration of the task will help us study forces before, after and identify if there was a lingering tap. A soft pad was used during the study, to allow for some degree of up-down movement to measure acceleration. Attempting to study forces on various surfaces may help in the addition of the force component of the device as it has an accelerometer built into it.

A decrease in the target distance in the double target tap is recommended as there was a considerable difficulty noted in performing the task by all groups tested. Fatigue may have resulted in a dilution of results in the HD patients.

The metronome task has generated a lot of data, which however failed to identify a significant pattern among the groups for the various frequencies measured. Changing the time duration and testing the subjects with the same order may yield better results, as there were differences noted between patients and controls in terms of mean frequencies.

10.6 Further work

Larger sample sizes of PD and HD subjects with subdivision of the main symptoms of PD and the stage of HD would be the next step in studying the validity of this device for the assessment of motor function as a clinical biomarker for these diseases. Retesting subjects to understand the learning effect on tapping (if any), and comparing other Parkinsonian syndromes to understand the specificity of the device are some of the future improvements I have in mind. As the software is in the form of an android app, it was programmed for a 7' Samsung Galaxy, Testing on larger Android devices with the same application (corrected for different dimensions) to study reproducibility would make this application easily accessible to other researchers and clinicians, who work towards establishing biomarkers in PD and HD.

Appendix

1. Information Sheet
2. Ethics approval information
3. Consent form

DEPARTMENT OF CLINICAL NEUROLOGY

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V 4.0

Patient Information Sheet

Response inhibition in health and disease

People with Parkinson's disease: behavioural experiments

Introduction

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Patients with certain types of neurological disorder can have difficulties in controlling their movements appropriately. We wish to gain insight into the reasons for this by examining aspects of movement control in healthy volunteers, people with Parkinson's disease, people with - or at risk of developing - Huntington's disease, and people with focal brain injury from stroke or surgery. We aim to do this by asking participants to perform simple tasks involving either

hand or eye movements in response to visual stimuli presented on a computer screen and measuring the speed and accuracy with which they respond.

Why have I been chosen?

You have Parkinson's disease, satisfy the criteria for participating, and have responded to our invitation letter.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

In one set of tests, you will be asked to sit in front of a computer screen and respond to visual stimuli (usually various small coloured shapes) briefly presented on the screen. You will be asked to respond to the stimuli either by pressing a button or by moving your eyes. If eye movement responses are required the position of your eyes will be monitored by a small infra-red tracker positioned either in front of you or on a headset. The tracker only looks at the eyes and does not record a video image of any part of your face. The experiment will consist of many individual trials grouped into blocks lasting about 6 minutes each. You will be invited to rest for as long as you like between blocks, and you may rest at any time during the experiment. The total length of the experiment will be about 1 hour. Detailed instructions about the task will be given to you before the beginning of the experiment. At the end of the experiment you will be asked a few simple questions about your symptoms and asked to make some simple movements in order to assess your condition clinically.
In another set of tests, you may be asked to make rapid hand movements from different positions to a pad. This time the position of you hand may be measured using another type of infra-red tracking system, while the force you generate is measured using a force-plate. The total length of this type of test will be about 1 hour.

What are the possible disadvantages and risks of taking part?

There are no known disadvantages or risks in taking part in this study.

Compensation for harm arising from an accidental injury and occurring as a consequence of your participation in the study may be covered by the University of Oxford.

If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against the University of Oxford.

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr Chrystalina Antoniades or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 743005, or the head of CTRG, Heather House <heather.house@admin.ox.ac.uk>.

What are the possible benefits of taking part?

Taking part is of no direct benefit to you. The information we get from this study may help us to treat future patients with neurological problems better.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it. **Responsible members of the University of Oxford or the Oxford Radcliffe Hospitals NHS Trust may be given access to anonymised data for monitoring and/or audit of the study to ensure we are complying with regulations.**

What will happen to the results of the research study?

The results of this study are likely to be published in scientific journals. You may request a copy of the published results if you wish. No personally identifiable information will be published.

Who is organising and funding the research?

The Wellcome Trust.

Who has reviewed the study?

The Wellcome Trust and The Hammersmith & Queen Charlotte's & Chelsea Hospitals Research Ethics Committee. **Ref. REC No. 04/q/0406/60; Date 02/09**

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UNIVERSITY OF OXFORD

Consent Form

Title of Project: Response inhibition in health and disease: behaviour

Professor Christopher Kennard & Dr Chrystalina Antoniades

Please initial box

☐ **I confirm that I have read and understand the information sheet dated 02/09 (version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.**

☐ I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

☐ **I understand that sections of any of my medical notes may be looked at by responsible individuals from University of Oxford or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.**

☐ I agree to take part in the above study.

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

4. Questionnaire HD

Serial Number:

1. **Name**:

2. **DOB:**

3. **Sex**:

4. **Education:**

5. **Occupation:**

6. **Handedness**: R/L

7. **Year of diagnosis:**

8. **Neurological History**: Y/N

9. **Other Medical History**: Y/N
   If yes, are you on any Medication? :

10**. History of Head injury**: Y/N
   If yes, was it associated with Loss of Consciousness? : Y/N

11. **History of Thyroid illness**: Y/N Medication:

12. **Family History of Neurological Illness**: Y/N
   If known, state:

13(Optional)**: Smoking**: Y/N If yes - No.per day _____
14(Optional): **Alcohol consumption**: Y/N
If No skip to Q.15
If yes, Drinks per week- 0-2, 3-5, >6
How many hours ago was your last drink?

15. **Coffee consumption**: No, Yes: 1-2 cups/day, Yes- 3-4 cups /days, Yes- More than 5

16. In general, when you dance or listen to music, can you **keep a beat** ? Y/N

17. Are familiar with using touchscreens? Y/N
If Yes: What do you use in particular?

18. Would mind if we contacted you for further info: Y/N
17. ID Number:
18. CAG repeats:
19. Repeats in Parents/Other Notes

5. Questionnaire PD

PD

1.**Patient ID**:

2. **DOB**:

3. **Sex**: M/F

4. **Handedness**:

4. **Diagnosed on**:

5. **Medication**:

6. **Last medication**:
Time:

8. **Predominant symptom**:

9. **UPDRS/UHDRS score**:

10. **Other Medical History**: Y/N
If yes, are you on any medication? :

11**. History of Head injury**: Y/N
If yes, was it associated with Loss of Consciousness? : Y/N

12. **History of Thyroid illness**: Y/N Medication:

13. **Family History of Neurological Illness**: Y/N
If known , state:

14(Optional)**: Smoking**: Y/N If yes - No. per day _____

15(Optional): **Alcohol consumption**: Y/N
If No skip to Q.13
If yes, Drinks per week- 0-2, 3-5, >6
How many hours ago was your last drink?

16. **Coffee consumption**: No, Yes: 1-2 cups/day, Yes- 3-4 cups /days, Yes- More than 5

17. In general, when you dance or listen to music, can you **keep a beat** ? Y/N

18. Are familiar with using touchscreens? Y/N
If Yes: What do you use in particular?

19. Would mind if we contacted you for further info: Y/N
If yes, Contact:

Phone:

20. **Hospital ID:**

21: **Notes:**

6. Programming protocol – 6 pages

Protocol:

Device: Android Device, Firmware Version 2.2

Task 1:

Repetitive Tapping with one finger on one target

The test begins with a tab for entry of patient ID and three buttons:

1. Test
2. Report
3. Export

Functions of the buttons:

Test : Begins/ Initiates the test cycle.

Report: To retrieve any report, if the relevant ID is entered.

Export: To export the details into a CSV to be saved onto the tapping device.

Patient ID tab: To enter the ID to either begin the test or retrieve a report.

Test Sequence.

1. Click test button.
2. Tapping target appears(A central circle, of diameter 60 mm with a central red ‘x’ mark to pin point the exact area to be tapped).
3. The central x mark would be situated at the centre of the white tapping target.
4. This tapping target is in the centre of the android tablet (equidistant from both edges in a landscape mode).
5. The subject would be required to tap on the device, and the test would be displayed in a landscape mode.
6. Tapping would have to be done with the forefinger of both hands, each hand at a time. First tapping would be performed with the less affected followed by affected hand in the case of patients. Dominant followed by non-dominant in the case of controls.
7. Instruction on screen: When you hear a beep, start Tapping as fast as possible, as consistently as possible on the red ‘x’ mark until you hear a beep which signals the end of the test.
8. Tapping begins once there is a sound, and tapping is to be done for 30 seconds, which is specified to the patient before the test begins.
9. The test ends with the second beep (after 30 seconds), following which a short report with the Number of taps, Mean ITI, S. D of the ITI, Mean Pressure, S.D Pressure, Mean and S.D. of the Displacement from the central tapping area.

10. Along with the above values there would be two buttons with the tags: Details,

    Details: When the details button is clicked, each tap, with its corresponding Pressure value, Inter-tap Interval(ITI), X, y, co –ordinates and Displacement will be listed.

    7. Each of the repetitive tests would be performed on both the right and left hand. If the patient ID is 1, the test performed with the dominant hand is D1, non-dominant hand is ND1.

8. When connected to a computer, the above details along with the patient ID can be downloaded.

Variables calculated:

1.Number of taps/Tap Count: It is defined by the number of taps the subject taps on the target area for the duration of 30 seconds.

2. ITI/ Inter Tap Interval: It is defined by the time between each tap, in milliseconds.

3. ITI Mean and S.D: It is defined by the mean ITI for all the taps in the 30 second time frame as well as its Standard Deviation (S.D).

4. Pressure: It is defined by the pressure exerted by the individual while tapping on the target .

5. Pressure Mean and S.D: The mean pressure values over a 30 second time frame as well as its Standard Deviation (S.D) are calculated.

6. Displacement: The co-ordinates of each tap (x,y) are measured and its distance from the co-ordinates of the central tapping area within the target are measured. The value of d (displacement) is calculated using the formula:

$$d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2}$$

7. Displacement Mean and S.D: The mean values of displacement and Standard deviation over a period 30 seconds.

2. Repetitive Tapping with one finger on two targets alternatively.

The test begins with a tab for entry of patient ID and three buttons:

1. Test
2. Report
3. Export

Functions of the buttons:

Test : Begins/ Initiates the test cycle.

Report: To retrieve any report, if the relevant ID is entered.

Export: To export the details into a CSV to be saved onto the tapping device.

Patient ID tab: To enter the ID to either begin the test or retrieve a report.

Test Sequence.

1. Click test button.

2. Two tapping targets separated by a distance of 20 cm (will appear on the screen and will be viewed on landscape mode on the device.
3. Tapping targets comprise of a central circle, of diameter 60 mm with a central red ‘x’ mark to pin point the exact area to be tapped.
4. Instruction on screen: When there is a beep, start tapping alternatively on the targets as fast as possible and as consistently as possible until you hear a beep.
5. The duration of the test would be 30 seconds.
6. Tapping would have to be done with the forefinger of both hands, each hand at a time. First tapping would be performed with the less affected followed by affected hand in the case of patients. Dominant followed by non-dominant in the case of controls.
7. The test ends with the second beep, following which a short report with the Number of taps, Mean ITI, S. D of the ITI, Mean Pressure, S.D Pressure, x, y co- ordinates and Displacement from the central tapping area.
8. Along with the above values there would be two buttons with the tags: Details,

   Details: When the details button is clicked, each tap, with its corresponding Pressure value, Inter-tap interval (ITI), Displacement will be listed.

8. Each of the repetitive tests would be performed on both the right and left hand. If the patient ID is 1, the test performed with the dominant hand is D1, non-dominant hand is ND1

9. When connected to a computer, all these details along with the patient ID can be downloaded.

Variables calculated:

1.Number of taps/Tap Count: It is defined by the number of taps the subject taps on the target area in a span of 30 seconds.

2. Right Count: Number of taps made on the right target in the span of 30 seconds.

3. Left Count: Number of taps made on the left target in the span of 30 seconds.

4. ITI/ Inter Tap Interval: It is defined by the time between each tap, in milliseconds.

5. ITI Average and S.D: It is defined by the average ITI for all the taps in the 30 second time frame as well as its Standard Deviation(S.D).

6. Pressure/Force: It is defined by the pressure exerted by the individual while tapping on the target .

7. Pressure Average and S.D: The average pressure values over a 30 second time frame as well as its Standard Deviation(S.D) are calculated.

8. Displacement: The co-ordinates of each tap(x,y) are measured and its distance from the co-ordinates of the central tapping area within the target are measured. The value of d (displacement) is calculated using the formula:

$$d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2}$$

9. Displacement Average and S.D: The average values of displacement and Standard deviation over a period 30 seconds.
10. Right Displacement: Displacement measured from the actual centre on the right target (Calculated only on taps made on the right target).
11. Left Displacement: Displacement measured from the actual centre on the left target (Calculated only on taps made on the left target).

3. Tapping in synchrony to auditory rhythm.

The test begins with a tab for entry of patient ID and two buttons to Start the Test and a report button.

Functions of the buttons:

Start: Begins/initiates the test cycle.

Report: To retrieve any report, if the relevant ID is entered.

Patient ID tab: To enter the ID to either begin the test or retrieve a report.

Test Sequence:

1. Click Test button.
2. Central target appears; 60 mm in diameter with a central red 'x' mark measuring 5 mm in diameter. Click Start
3. Test is initiated with a beep, and Start instruction. The rhythm is set by frequencies of 1, 1.5, 2, 4 and 5 Hz each lasting for 10 seconds each with a break of 5 seconds in between. The last two would be randomized in such a way that 4 or 5Hz will never be the first. In summary, the rhythm would be at any of the frequencies, whose order would be random, which will however never have the fastest frequencies (4 or 5Hz) first.
4. The break of 5 seconds requires the subject to continue tapping at the same frequency as the last heard one, in the absence of the auditory cue.

5. Test sequence summary: Test< Target Appears < Instructions given< Click Start< Frequency 1 begins….. 10 seconds< No sound for 5 seconds<Patient required to tap at the same rhythm for 5 seconds<Frequency 2 starts< Patient required to tap at Freq2……..Freq4+5 seconds silence< Continue to tap at Freq 4< Long Beep<Target vanishes.
6. Test report Button appears, when clicked it would give us values of variables.
7. Number of taps in each block, Mean Frequency for each frequency block with S.D, Accuracy w.r.t to the Frequency in the form of a percentage for each block.

Variables:

1. Number of taps: Number of taps for each block,: Freq1, Break 1, Freq 2, Break 2, Freq3, Break 3, Freq4 ,Break4.
2. Frequency, Mean frequency and S.D of frequency for each block: Freq1, Break 1, Freq 2, Break 2, Freq3, Break 3, Freq4 ,Break4.
3. Accuracy, Mean Accuracy and S.D Accuracy: Accuracy of the tapping w.r.t to Frequency of each block

4. Pro-tap Task

The test begins with a tab for entry of patient ID and two buttons to Start the Test and a report button.

Functions of the buttons:

Start: Begins/ Initiates the test cycle.

Report: To retrieve any report, if the relevant ID is entered.

Patient ID tab: To enter the ID to either begin the test or retrieve a report.

Test Sequence:

1. Click Test button.
2. Central fixation square (1'X 1') appears, another button called start is labeled just below it. Once the start button is clicked, after a pause of 2 seconds a new target appears, on either the right or the left side.
3. The new target is of the same dimensions as the fixation square.
4. The new/peripheral target appears after the fixation square disappears and a gap follows(200ms).
5. In summary, the sequence is Fixation square disappears, peripheral target appears, target clicked, fixation square appears.
    - Time to be defined. Fixation appearance and disappearance (Random values between 0.5 and 1.5 seconds).
6. The subject places their forefinger on the fixation square, and the target appears either on the right or left randomly, but with equal trials. A total of 40 trials (20 right and left) will be done.

7. There will be no landmarks for the target positions, the design would be as far apart as possible on the tablet.

Variables:

1. The test output will be in the form of Response time (RT) and ErrorRates (ER).
2. Response time (RT) is defined as the amount of time taken for the subject to tap the target on its appearance. The time will be taken as follows, time from the second the finger is removed from the fixation stimulus to the time taken to tap the peripheral stimulus.
3. ErrorRate: Is the percentage of correct trials performed, i.e, Number of times the subject taps the target on the same side/total number of times the target appears on that side X 100.
4. Average RT and S.D: The Average RT and Standard deviation in the 48 trials performed.
5. ErrorRate D and S.D: Errorrate on the Dominant side as well the standard deviation.
6. ErrorRate ND and S.D: ErrorRate on the non-dominant side as well as the standard deviation.

5. **Anti-tap Task**

The test begins with a tab for entry of patient ID and two buttons to Start the Test and a report button.

Functions of the buttons:

Start: Begins/initiates the test cycle.

Report: To retrieve any report, if the relevant ID is entered.

Patient ID tab: To enter the ID to either begin the test or retrieve a report.

Test Sequence:

1. Click Start button.
2. Fixation Square appears (1'X1'). The subject is required to place the finger on it. The peripheral target appears on either the right or left simultaneous to the disappearance of the fixation square. The subject is required to tap the opposite side of the peripheral target. There will be 30 trials each. The tapping would need to be done on the opposite side without a landmark for tapping.
3. The next set of trials continuous with the same task is the appearance of landmarks on the opposite side of the target.
4. The order of landmarks and trials sans landmarks would be randomized.
5. At the end of 15 +15 trials, right and left equally. The test would come to and end with the disappearance of all targets and a beep.

Variables:

1. Response time: Amount of time taken to move the finger from the fixation target to the opposite direction of the peripheral stimulus and tapping it on the opposite area of the device.
2. ErrorRate: Percentage of wrong trials performed, i.e, Number of Taps on the same side/Number of times the target appears on the same side X 100.
3. Response time Mean and S.D: Mean of the response time and standard deviation among all 40+40 trials performed.
4. ErrorRate Mean and S.D: Mean Error Rate and Standard Deviation with the Dominant and non dominant hand.

6. Conflict tapping task:

The test begins with a tab for entry of patient ID and two buttons to Start the Test and a report button.

Functions of the buttons:

Start: Begins/initiates the test cycle.

Report: To retrieve any report, if the relevant ID is entered.

Patient ID tab: To enter the ID to either begin the test or retrieve a report.

Test Sequence:

1. Click Start.
2. Central fixation square appears (1X1”), simultaneously a target appears to the right, there is a red/green light above it.
3. A visual cue appears on the right or left in the form of a red or green light.
4. The visual cue appears immediately after the fixation square appears. When the central cue is red and the visual cue on the right or left is also red, the subject is required to tap on the same side of the appearance of the target.
5. When the central cue is red, and the peripheral visual cue is green the subject is required to tap on the opposite side as the new visual cue, ie on the tapping space below the new visual cue. Basically, if both the colors central and peripheral are the same, the subject would be required to tap on the same side. If the colors were different, the subject would be required to tap on the opposite side.
6. There would be 60 trials totally, 30 each.
7. The subject is required to place their forefinger of the dominant hand on the fixation target and tap to the right or left of the fixation square.
8. The response time would be recorded as the amount of time taken for the finger to move from its position (fixation square) to the tapping area(which has no landmarks), which is the right or left of the fixation square.

Variables:

1. Response time for each tap:
2. Response time for correct taps:
3. Response time for incorrect taps:
4. Error-rate:
5. Average RT, S.D
6. Error-rate and S.D

7. **Testing Instructions:**

Materials:

1.Hand tapping tablet

2. Questionnaire

3. Patient Information sheet

4. Informed Consent form

5. Wrist Pad

6. Edinburgh Inventory Scale

Hand tapping tasks:

1. Repetitive Tapping – Single finger.
2. Repetitive Tapping – Double finger.
3. Tapping to Auditory tones.
4. Pro – Tap Task
5. Anti – tap task
6. Conflict task

Instructions:

Please be seated comfortably.

Place arm on the table, with the wrist on the wrist pad, such that the fingers reach the tablet in a comfortable manner.

The study will take about half an hour. I will be recording timings for taps on this tablet, and will administer 6 tests to you.

You will be required to tap with both your hands, one at a time. I will instruct you accordingly.

First I will let you practice on the tasks, to let you familiarize yourself with the device and the tests.

First task: The task has a central white circle, which also has a red cross mark within it. I would require you to tap as fast as possible, and as consistently as you can, for a period of 30 seconds. The taps would have to be on the white circle, try

as much as possible to tap on the red cross mark. The end of the test is signalled by a beep, after which you will be required to stop tapping.

For practice: Please tap on the central white circle. Try to tap as much as possible on the red cross mark. Please tap as fast as possible for 10 seconds.

Second task: The task has two white circles, separated from a distance. I would require you to tap on these two circles alternatively as fast as possible for a period of 30 seconds. Tap on the white circles, and try as much as possible to tap on the red cross mark. The end of the test is signalled by a beep, after which you will be required to stop tapping.

For practice: Please tap on the two white circles, alternatively. Try to tap as much as possible on the red cross mark. Please tap as fast as possible for 10 seconds.

Third task: The task involves tapping to auditory tones, playing at different rates. There are 5 different tapping rates each lasting 10 seconds each, with rest blocks of 10 seconds in between. The task would begin with one tapping rate, and I would require you to tap in time with those tones/beeps. After which, there us a gap of 10 seconds, where in there would be no beeps/sounds. During this time period, I would require you to tap at the same rate as the last 10 seconds. There would be 5 sets of the same.

For practice: Please tap on the central circle in time with each beep. Try to remember the rhythm at which you tapped and tap at the same rate for the next 10 seconds, when you do not hear any sound as well.

Fourth Task: This task would test your reaction time. There is a central square, place your forefinger on it, and hold down(I will demonstrate). When you see a see a new square appear to the right or left, tap it as soon as you see it. I would like to see how quickly you would react to this new square. There will be 40 trials of the same, after which the test will come to an end.

For practice: Place your forefinger on the central square, and hold down. When this new square appears, tap it as soon as you see it. Repeat. Continue the same for the next 10 seconds.

Fifth Task: This task would test your reaction time. There is a central square, place your forefinger on it, and hold down (I will demonstrate). When you see a see a new square appear to the right or left, do not tap on the new square, instead tap on the OPPOSITE side of the new square. However, just like the previous test, tap the opposite side as soon as you see the new square. I would like to see how quickly you would react to this new square. There will be 40 trials of the same, after which the test will come to an end.

For practice: Place your forefinger on the central square, and hold down. When this new square appears, tap the opposite side of the screen (black area). Repeat. Continue the same for the next 10 seconds.

Sixth Task: This task is similar to the last two tests. There is an additional red or white dot, which determines which side you should tap. Place your forefinger on the Central Square and hold down, when you see that a new square appears, tap. When the new square appears, if there is a green dot above it, tap on the square. If there is a red dot, tap on the opposite side of the square.

For Practice: Place your forefinger on the central square, and hold down. When this new square appears, and there is a green dot above it, tap the square as soon as you see it. When this new square appears, and there is a red dot above it, tap the opposite side of the screen (black area). Repeat. Continue the same for the next 10 seconds.

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