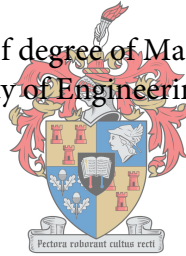


PANDAS: Paediatric Attention-Deficit Hyperactivity/Disorder Application Software

by

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Thesis submitted in fulfillment of degree of Master of Mechanical and Mechatronic
Engineering in the Faculty of Engineering at Stellenbosch University



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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder that impairs social, academic, and occupational functioning in children, adolescents and adults. It is estimated that approximately as high as 10% of South African children have ADHD. Some dilemmas are however present in terms of the treatment of the disorder: firstly, there are no risk-free methods for its treatment and secondly, no fully objective diagnostic assessments exist. To date, very few quantitative methods have been successfully implemented. It is therefore necessary to further investigate methods that objectively diagnose, treat, and manage the disorder. The aim of the study is thus to develop a novel method that can be used as an aid to provide screening of ADHD. The method proposed is the form of a tablet-based game with underlying algorithms. The objective of the method is to differentiate between an ADHD individual versus a non-ADHD individual, based on the way they play the game. A beta-testing phase was done and comprised of 30 children (19 non-ADHD and 11 ADHD) between the ages of 4 and 18 years old. The machine learning model that was used was linear support vector machine (SVM). Two datasets were used: 1) game-play dataset which included data such as task completion time and number of mistakes made and 2) accelerometer data set from the tri-axial accelerometer. A feature set was extracted from these two datasets and the best features were selected using sequential forward selection. These best features were then used for developing the classifier. A test set accuracy of 85.7% was achieved. Leave-one-out cross-validation (LOOCV) was performed and its accuracy was 83.5%. An overall classification accuracy of 86.5% was achieved. For the application of a screening tool, sensitivity was deemed an important metric and. The model achieved a sensitivity of 75% which was seen as acceptable. The results of the classifier were indicative that a quantitative tool could indeed be developed to screen for ADHD.

Uittreksel

Aandagafleibaarheid-hiperaktiwiteitsindroom (ADHD) is 'n algemene neuro-psigiatriese versteuring wat sosiale-, akademiese- en beroepsfunksionering belemmer by jong kinders, tieners en volwassenes. Dit is beraam dat ongeveer as meer as 10% van Suid-Afrikaanse kinders ADHD het. Sommige dilemmas is egter teenwoordig met betrekking tot die behandeling van die versteuring: eerstens is daar geen risiko-vrye metodes van behandeling nie en tweedens bestaan daar geen volledige objektiewe diagnostiese assessering nie. Tot vandag toe is daar baie min kwantitatiewe metodes wat suksesvol geïmplementeer is. Daarom is dit dus nodig om verdere metodes te ondersoek wat die versteuring objektief kan diagnoseer, behandel en bestuur. Die mikpunt van die studie is dus om 'n nuwe metode te ontwikkel wat gebruik kan word as 'n hulpmiddel om vinnige en akkurate keuring van ADHD te voorsien. Die voorgestelde metode is in die vorm van 'n elektroniese tablet-gebaseerde speletjie met onderliggende algoritmes. Die doel van die metode is om te onderskei tussen 'n individu met ADHD en 'n individu sonder ADHD, gebaseer op die manier hoe hulle die speletjie speel. 'n Beta-toets fase wat bestaan uit 30 kinders tussen die ouderdomme van 4 en 18 jaar oud was gedoen (19 met ADHD en 11 sonder ADHD). Die masjienleer model wat gebruik vir die studie was support vector machine (SVM). 'n Test akkuraatheid van 85.7% was behaal. Leave-one-out cross-validation was gebruik word en 'n akkuraatheid van 83.5% was behaal. Ter afsluiting was dit gedemonstreer dat 'n kwantitatiewe hulpmiddel ontwikkel kan word vir die keuring van ADHD.

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Dedications

To my late father, Willy Mwamba, a great man.

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Chapter 1

Introduction

1.1 Background

Attention-deficit/hyperactivity disorder (ADHD) is a brain disorder marked by an ongoing pattern of inattention and/or hyperactivity-impulsiveness that interferes with functioning or development [1]. It affects a great number of people worldwide and is especially prevalent in children although adult prevalence is increasingly gaining attention. The exact origin of the disorder is uncertain and complex [2]. ADHD is one of the most common cognitive disorders, yet its diagnosis relies almost exclusively on subjective assessments of perceived behaviour [3]. This may result in inconsistent diagnoses. For example, while one specialist may perceive a specific symptom as severe, another one could perceive that same symptom as acceptable. Therefore, as the number of assessed symptoms increases, so does the complexity of the diagnosis.

ADHD is found mainly in children and adolescents. It is also found in adults, especially if they were previously diagnosed during childhood. The worldwide prevalence of ADHD is approximated by Polanczyk et. al. as 5%. Although prevalence data in South Africa is incomplete, it is estimated to be as high as 10%, similar to that of the United States of America with regards to youths.

The current diagnostic methods present some unresolved dilemmas. Firstly, there is a potential risk of overdiagnosing patients. Secondly, males are more likely to be diagnosed compared to females of the same age [4]. Finally, objective diagnostic methods are scarce. Although there are other unresolved dilemmas around the disorder, the previously mentioned ones are good examples that highlight the complexity of ADHD diagnosis. Generally speaking, diagnosis relies on the specialist's experience as well as whether or not a specific patient resembles the specialist's perceived concept of a prototypical ADHD patient. Furthermore, since ADHD is more prevalent in males, specialists may become biased to perceive them as prototypical patients. This therefore re-

sults in males being more readily diagnosed, and possibly overdiagnosed, than females [2].

In addition to diagnosis, other challenges of ADHD are its treatment and management. For children between the ages of 6 and 18 years old, symptoms are typically identified in a classroom setting. Specialists such as child psychologists will then interview the whole family and provide the parents and the teacher(s) with questionnaires called rating scales. Furthermore, the patient undergoes a series of psychometric tests. Based on the results of the rating scales as well as those of the psychometric tests, a thorough diagnosis is made and a treatment plan is drawn up. The patient then goes for follow-up sessions, generally after every 6 months. This process represents the ideal case of identifying and diagnosing ADHD. In reality, however, many schoolchildren are not identified as potential ADHD patients. This presents the need for a screening tool that may help identify the disorder from an early stage, such as in a classroom setting.

1.2 Problem Formulation

There are no guaranteed methods for the treatment of ADHD, nor are there any objective tests to diagnose the disorder. To date, very few quantitative techniques exist whereby the diagnosis or drug effectiveness can be demonstrated with any degree of accuracy. There is therefore an increasing need for more objective diagnosis and more effective treatment and management of the disorder. In this study it was hypothesised that a person could be screened for ADHD through the use of objective and quantitative software algorithms.

1.3 Aim of Research and Objectives

The aim of the study was to develop a novel method that provided quick screening for the hyperactive subtype of ADHD. A concurrent study was done where the screening is done for the inattentive subtype of ADHD. The output of the study was a diagnostic aid rather than a diagnostic tool. The final diagnosis is still to be issued by a specialist. The overall objectives were broken down as follows:

- * Identify measurable parameters for ADHD based on DSM-5 criteria and psychometric tests;
- * Design and develop diagnostic-aiding software tool;
- * Perform beta-tests and gather data;
- * Perform clinical trials and gather data;
- * Use the gathered data to develop a predictive models;

1.3.1 Game Design

Mobile tablets have become popular and very accessible to the general public with the current advances in technology. Playing games on tablets has become a ubiquitous activity. The software tool was developed in the study was based on the fact that tablet games are popular and enjoyable. Although the aim of the tool was to aid diagnoses, it had an element of leisure, thus making it more engaging for the subjects. To keep in line with the development of a novel software method, it was decided that the tool should be in the form of a tablet-based game. Due to the high expectations of the game design, and to the fact that the actual game design was not part of the scope of the study, gaming developers were outsourced and given a design specification that met the following objectives:

- * Implement measurable parameters;
- * Develop an overarching storyline;
- * The duration of the game must be 2 to 3 minutes;
- * Provide some form of scoring system based on the performance of the user;
- * Match the standard of current tablet-based games in terms of aesthetics and ease of use;

1.3.2 Data-Processing Model Design

The purpose of the data processing algorithms underlying the game interface was to analyse and process game data. The objectives of the algorithms are the following:

- * Gather real-time data (from the parameters) during game-play;
- * Provide storage structure for the data;
- * Clean the data (pre-processing);
- * Create a statistical model with the data;
- * Make predictions based on the model.

1.4 Motivation

It is desirable to develop a screening tool that serves as a diagnostic aid to specialists. The most critical part of ADHD diagnosis is early detection. This becomes difficult in large and busy classroom environments. However, with a screening tool, teachers and school psychologists can test all the children in

a school. In this manner, even the non-prototypical ADHD patients can be identified. Additionally, specialists can use the tool during the early stages of consultation.

Furthermore, it is desirable to ascertain the effectiveness of medication to determine the correct diagnosis of ADHD in order to limit side effects due to drug overdose; to curb costs; to determine whether the dose should be increased as a child grows older; and to determine which drug works more effectively (e.g. stimulant vs non-stimulant types of drugs). The use of a screening tool helps make this possible since its results are now quantitative, as opposed to the qualitative results of the traditional methods. The use of quantitative results will in turn enable treatment success and progress to be tracked.

The study is valuable because its outcome could potentially yield a product that will have a positive impact on society. In addition to the potential of impacting the lives of patients that suffer from the disorder, the research will add value to the field of ADHD. As will be shown in literature, there are very few successful and fully operational objective diagnostic tools.

1.5 Thesis Layout

The thesis is divided into 7 chapters. Each chapter begins with an introduction wherein the main theme(s) of that chapter is conveyed, as well as the sub-themes that will be discussed. Sub-themes will be presented in different sections and the last section of a chapter provides a summary and synthesis. This structure is followed throughout the thesis, with the exception of the introductory and concluding chapters which follow their own structures.

Chapter 2 presents a literature review where ADHD is defined from a clinical point of view. The sub-themes include current diagnosis, existing computerised tools and existing sensor-based tools. Chapter 3 explains the design specification of the software tool. This comprises of two main themes, the game design and the data-processing model design. The design specification for the game touches on topics such as device selection, functionality and aesthetics. The study methodology is given in Chapter 4 while Chapter 5 is dedicated to machine learning. The chapter includes a theoretical explanation of the machine learning models that were chosen, as well as how those models were applied to the datasets. The results of the machine learning performance are presented as a conclusion to the chapter. A discussion and analysis of the results are given in Chapter 6. Finally, conclusions are drawn and recommendations are given in Chapter 7.

Chapter 2

Literature Review

There are various definitions that have been given to ADHD that are found in literature. The key aspect that can be drawn from these definitions is that ADHD has a great impact on behaviour. The definition of the term “behaviour” is given as *the way in which one acts or conducts oneself, especially towards others* [5]. Therefore, by definition, it can be said that ADHD is a multidimensional disorder that affects the patient on a number of levels; such as academically, socially, and personally. Furthermore, as will be discussed, the diagnosis is tiresome and expensive, with the estimated financial burden being \$3020 per annum for an adult [6]. The following chapter will present findings and research pertaining to ADHD and its diagnosis to date. The literature review will begin with a discussion on the aetiology. The importance of the aetiology is that it explains the proposed origins and causes of ADHD. Furthermore, examples of factors that may cause ADHD are presented. The next topic that is covered is an idealised version of the current diagnostic procedure in South Africa. Thereafter, continuous performance testing (CPT) will be explained and existing computerized tests that use this method will be presented. As an indication of the accuracy of these tests, studies that have used the tests will also be presented, as well as their shortcomings. Finally, the most recent objective assessment tools will be shown.

2.1 Aetiology

The aetiology of ADHD still remains unclear [2; 7; 8; 9]. The probability that one will develop ADHD is not based on a single risk factor but a combination thereof. Risk factors typically include genetics, environmental factors, neurobiological factors, and psychosocial factors. Each of these risk factors are discussed subsequently in more depth.

2.1.1 Genetics

Similar to most psychiatric disorders, ADHD has a familial nature. Genetic risk factors can be inherited from one generation to the next, although this is not always necessarily true: some genetic risk factors are not passed on [10]. In support of the familial nature of the disorder, a study conducted by Faraone et al. concluded that the first degree relatives of a person suffering from ADHD are two to eight times more likely to suffer from ADHD than relatives of a person without ADHD [9]. Another family study found the same results: a two to eightfold increase in the risk of developing ADHD when a parent or sibling suffers from ADHD compared to the normal population [11]. To further support this theory, a study was done where three family studies were analysed [7]. The results of those three family studies are shown in Figure 2.1. It can be seen that the occurrence of ADHD in first-degree family members of children with ADHD was almost four times as high as the non-ADHD control group.

Another genetic factor that is observed in many studies is gender. According to the worldwide prevalence rate, it was seen that the percentage is higher in males. The exact reasons for the higher occurrence are not fully understood. Typically, specialists are more biased to diagnose males as having the disorder because they resemble their prototypical patient. Overdiagnosis then becomes a potential risk [12]. It has been found that more boys receive treatment than girls, where the male-to-female ratio ranges from 5:1 to 9:1 [13]. However, population studies show that the male-to-female ratio of ADHD patients is only 3:1 [14].

2.1.2 Environmental Factors

A wide range of environmental factors are associated with ADHD, although not all of them are definitely causal [10]. Environmental risks can be classified

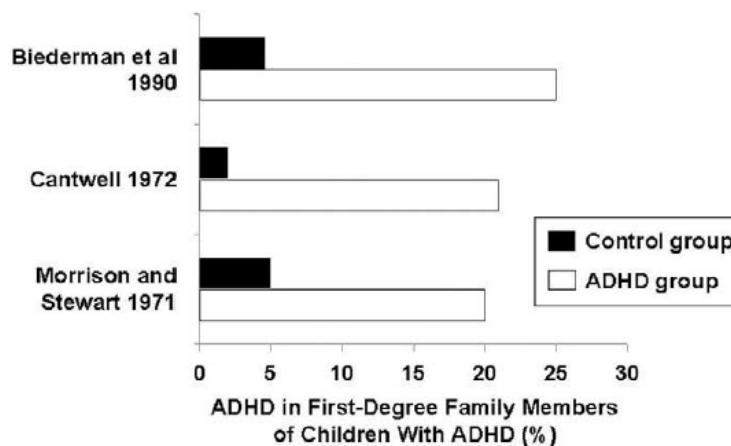


Figure 2.1: Family Studies in ADHD [11]

as pre/peri natal, psychosocial, dietary or environmental toxins [2; 10]. The most common prenatal risk is maternal smoking. It has been shown that the risk of having ADHD is related to the intensity of maternal smoking [15]. Some studies have shown the child is at an increased risk when the mother uses alcohol moderately [16]. According to studies the inattention subtype of ADHD is associated with prematurity and low birth weight [17]. However, This risk is not necessarily causal since prematurity is also caused by other underlying factors. Finally, brain injury can also cause dysfunction in important brain regions.

The mental health of a child can be associated with certain indicators such as poverty and family adversity. It has been shown that children that are subject to maltreatment and a harsh parenting style are more susceptible to being diagnosed with ADHD [10]. Caution must be taken when correlating psychosocial adversity with ADHD because the risk could either be a cause or a consequence of the disorder. Parent-child conflict, for example, could be a consequence of the ADHD and not necessarily the cause thereof.

Most dietary risks are associated with deficiencies in certain important dietary components. Studies generally show that although diet impacts the neurodevelopment of a child, not enough evidence is present to determine the extent to which diet causes ADHD [2; 10]. In fact, diet becomes more important in the treatment and management of ADHD and not as much in causing it. Toxic industrial products like polychlorinated biphenyls (PCBs) are environmental contaminants. Studies have reported that exposure to PCB negatively impacts memory, cognitive functions, and response inhibition [18]. These impairments can easily be related to ADHD. Similarly, it has been found that lead exposure also affects cognitive functions as well as alertness and vigilance [18].

2.1.3 Neurobiological Factors

The neurobiology of ADHD is not fully understood. Most studies support the hypothesis that there is a relationship between the disorder and dysfunction of the prefrontal cortex [7]. This region of the brain allows for inhibitory control, which ADHD patients usually lack to some extent. Structural magnetic resonance imaging (MRI) studies have shown that with ADHD patients, as opposed to the normal population, there was a decrease in total brain volume and more specifically, in the regions of the brain involved with cognitive control [19].

With regards to motor response, it is observed that children with ADHD make both quick and long motor responses [7]. Here quick motor response are associated with impulsiveness and long motor responses are associated with delayed reaction in the response. The observed response variability is often

attributed to the caudate nuclei. Studies show that the caudate nuclei has a smaller volume in children with ADHD [19]. The implication of this reduced volume is that although a person with ADHD might formulate a response using the appropriate level of executive function, they might still have trouble executing the motor component of that action [19].

The cerebellum is the part of the brain that is responsible for functions such as time perception and time discrimination. When performing tasks involving time, children with ADHD show deficits. It is becoming increasingly accepted that ADHD is a disorder of motor control and timing [20]. Deficits in ADHD patients are caused by complex combinations of genetics and environmental factors, while neurobiological dysfunction is patient specific.

2.2 Diagnosis

Proper treatment of ADHD requires an accurate diagnosis. There currently exists no totally objective diagnostic method or test, although there are a few that are near-objective, as will be discussed in subsequent sections. Therefore, a large part of a diagnosis is made based on clinical criteria defined by the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) or by the International Classification of Mental Diseases (ICD-10) [2]. Both of these tools are accepted and used worldwide and they provide a baseline for defining symptoms for various mental disorders, ADHD being one of them. The two standards use different methods and cover different variations of the ADHD: while DSM-5 is able to identify different subtypes of ADHD, ICD-10 focuses on a much narrower range called hyperkinetic disorder which puts more emphasis on hyperactivity. DSM-5 is currently used in South Africa. An important aspect of the diagnosis is the clinical interview with parents, the child, and other significant members in the child's life. This is necessary since the child might not be able to report symptoms accurately as opposed to a parent or teacher who has had an opportunity to observe the child. At this stage, rating scales may be used by parents, teachers and specialists. Rating scales are discussed further in section 2.2.2. In addition to rating scales, psychometric test batteries and intelligence tests are used in the diagnosis process. These are discussed briefly in section 2.2.3.

2.2.1 DSM-5 Criteria

DSM-5 identifies two classifications of ADHD: 1) inattention and 2) hyperactivity or impulsivity. Each classification is defined by nine symptoms. When working with persons under the age of 17 years old, six or more symptoms have to be persistently present in the last six months (from the time of evaluation) to a degree that is inconsistent with developmental level and negatively impacts directly on social and academic/occupational activities. For individ-

uals older than 17 years old, at least 5 symptoms need to be present. The symptoms/criteria for both classifications are shown in Table 2.1. In addition to identifying six or more symptoms in a person, other factors must be analysed. One of the factors is that the symptoms must be present in two or more settings (for example, at home and at school). Another factor is that several of the symptoms must have been present prior to the age of 12 years old (when applicable). Finally, there must be clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

Table 2.1: DSM-5 Criteria for ADHD

	Inattention	Hyperactivity/Impulsivity
1.	Fails to give close attention to details/makes careless mistakes	Often fidgets with or taps hands or feet or squirms in seat
2.	Difficulty sustaining attention	Often leaves seat in situations when remaining seated is expected
3.	Does not listen when spoken to directly	Often runs about or climbs in situations where it is inappropriate
4.	Does not follow through on instructions and fails to finish tasks	Often unable to play or engage in leisure activities quietly
5.	Difficulty organizing tasks	Often “on the go” acting as if “driven by a motor”
6.	Avoids/dislikes tasks that require sustained mental effort	Often talks excessively
7.	Loses things necessary for tasks	Often blurts out an answer before a question has been completed
8.	Easily distracted by extraneous stimuli	Often has difficulty waiting his or her turn
9.	Forgetful in daily activities	Often interrupts or intrudes on others

DSM-5 identifies three subtypes of ADHD, each with an associated level of severity, where the levels of severity are specified as mild, moderate or severe. The three subtypes of ADHD are listed as follows:

314.01 (F90.2) Combined presentation: Both the inattention and hyperactivity impulsivity criteria are met for the past 6 months.

314.00 (F90.0) Predominantly inattentive presentation: The inattention criterion is met but the hyperactivity-impulsivity criterion is not met for the past 6 months.

314.01 (F90.1) Predominantly hyperactive/impulsive presentation: The hyperactivity-impulsivity criterion is met but the inattention criterion is not met over the past 6 months.

2.2.2 Rating Scales

Rating scales are useful in assisting the diagnosis process. Various rating scales are found and can be used by parents, teachers, and specialists. Their purpose is to generate an objective assessment that is based on the child's behaviour, social interaction and emotional state. Examples of scales include the Swanson, Nolan and Pelham scale (SNAP), the Swanson, Kotkin, Agler, M-Flynn and Pelham scale (SKAMP), and the Connors' parent, teacher, and adolescent self-report scales, shown in Figure 2.2 [21]. These scales focus on classroom behaviour and performance. The Vanderbilt scale, shown in Figure 2.3 [22], takes into account classroom behaviour as well as comorbid conditions [8; 23].

Connors Parent Questionnaire				
Name of Child: _____		DOB: _____		
Name of Parent Completing Form: _____				
Please answer all questions. Beside each item below, indicate the degree of the problem by a check mark.				
	Not at all.	Just a little.	Pretty much.	Very much.
1. Picks at things (nails, fingers, hair, clothing).				
2. Sassy to grown-ups.				
3. Problems with making or keeping friends.				
4. Excitable, impulsive.				
5. Wants to run things.				

Figure 2.2: Extract of Connors Scale [21]

NICHQ Vanderbilt Assessment Scale – PARENT Informant*				
Today's Date: _____		Child's Name: _____		Date of Birth: _____
Parent's Name: _____		Parent's Phone Number: _____		
Directions: Each rating should be considered in the context of what is appropriate for the age of your child. When completing this form, please think about your child's behaviors in the past <u>6 months</u> .				
Is this evaluation based on a time when the child <input type="checkbox"/> was on medication <input type="checkbox"/> was not on medication <input type="checkbox"/> not sure?				
Symptoms	Never	Occasionally	Often	Very Often
1. Does not pay attention to details or makes careless mistakes with, for example, homework	0	1	2	3
2. Has difficulty keeping attention to what needs to be done	0	1	2	3
3. Does not seem to listen when spoken to directly	0	1	2	3
4. Does not follow through when given directions and fails to finish activities (not due to refusal or failure to understand)	0	1	2	3
5. Has difficulty organizing tasks and activities	0	1	2	3
6. Avoids, dislikes, or does not want to start tasks that require ongoing mental effort	0	1	2	3
7. Loses things necessary for tasks or activities (toys, assignments, pencils, or books)	0	1	2	3

Figure 2.3: Extract of Vanderbilt Scale [22]

Although rating scales are a very useful element of the diagnosis, they can include up to 90 questions. It can therefore be argued that there is some subjectivity in answering so many questions as opposed to having fewer questions. In a 2012 survey conducted by NeuropsychologySA, a website that aims to bring information to the neuropsychology community of South Africa, 20% of the the psychologists and registered counsellors that work with ADHD indicated that their preferred rating scale was the Connors Comprehensive Behaviour Rating Scales. This was the most popular rating scale by far due to its more compact and direct form.

While there may be a wide range of rating scales available, each specialist may have his/her own preference as to which one to use, based on their experience. That being said, there is no specific “rule” as to which scale to use. The general format of rating scales is similar to the figures shown. It comprises of a series of symptoms and observed behaviours and for each one the parent, teacher or specialist categorises its occurrences based on a scale such as: Never–Occasionally–Often–Very Often. Hence the term “rating scale”. The details of the parents and the child are also usually required as well as whether or not the child is on medication. A scoring system is also provided, based on the number of questions for each occurrence and this classifies the type of disorder the child may have, if any.

2.2.3 Neuropsychological Tests

Psychological tests are often used when diagnosing ADHD. However, they do not provide sufficient specificity to give insight as to what is causing the symptoms. Therefore, to provide a more comprehensive diagnosis, neuropsychological tests are used. The tests consist of tasks that are specifically designed to measure a psychological function known to be linked to a particular brain structure or pathway [24]. They provide specificity into which underlying neurological processes are causing the symptoms. Neuropsychological tests may also be used to better understand the aetiology of a disorder, as well as a means for testing intelligence.

There exists a wide range of neuropsychological tests and they evaluate one or more of the following ten skills: 1. attention and concentration, 2. verbal and visual memory, 3. auditory and visual processing, 4. visual-spatial functioning, 5. language and reading skills, 6. sensory development and sensory integration, 7. gross and fine motor development, 8. social skill development, 9. executive functioning and 10. emotional and personality development. According to NeuropsychologySA, the most popular test was the Bender-Gestalt Test that is used by 28% of the psychologists and counsellors that were surveyed [25]. The rest of this section describes six common tests that are used in the diagnosis process.

Bender-Gestalt Test

The Bender-Gestalt Test is a tool used for the evaluation of visual-motor functioning and visual perception skills. This test is helpful in diagnosing brain injury and proper functioning of the brain. Some of the parameters that are measured include visual maturity, visual motor integration skills, style of responding, reaction to frustration, ability to correct mistakes, planning and organizational skills and motivation. The test is administered by pencil and paper. Nine geometric figures are drawn in black and these figures are shown to the subject one at a time. The subject is then asked to copy the figure on a blank sheet of paper, as precisely as possible. An eraser is made available to correct mistakes but no mechanical tools, such as rulers, may be used. Figure 2.4 [26] shows an example of the test. On the left pane, the nine geometric shapes are presented. The right pane corresponds to what was drawn by a subject during the test. One of the reasons why this test is popular is the short amount of time required to run the test.

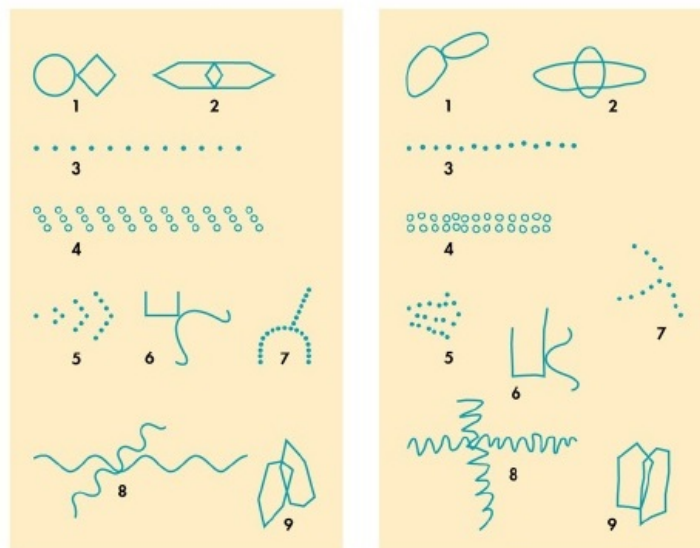


Figure 2.4: Bender-Gestalt Test [26]

Weschler Intelligence Scale for Children

The WISC test was developed by Dr. D. Weschler according to whom the definition of intelligence was described by an individual's ability to adapt and constructively solve problems in the environment [27]. Weschler's approach was that intelligence should be measured in terms of performance rather than capacity [27]. The WISC test provides information regarding a child's cognitive functioning as well as IQ scores. The duration of the test is between 65 and 80 minutes and consists of 10 core subtests and 5 additional subtests [27]. The age range is six years old to 16 years and 11 months old. Adult

and pre-school Weschler tests are also found and have a similar structure to the WISC test. The following 4 indices are measured by the WISC test: 1. Verbal Comprehension Index (VCI), 2. Perceptual Reasoning Index (PRI), 3. Working Memory Index (WMI), 4. Processing Speed Index (PSI).

Senior/Junior South African Individual Scales (SSAIS/JSAIS)

The Senior and Junior South African Individual Scales tests are a battery of tests that comprise of 22 tests that assess intelligence and cognitive ability. According to the previously mentioned survey, the JSAIS tests were the most popular intelligence tests, where 26% of the interviewed psychologists.

Continuous Performance Tests

Continuous performance tests or continuous performance tasks (CPT) measure a person's sustained attention. The term sustained attention refers to the ability to keep a consistent focus through a period of time, while external stimuli are present. It is accepted that CPT is the most frequently used measure of attention in both practice and research [28]. An example of a computerized CPT test is the Conners Continuous Performance Test 3rd edition (Conners CPT 3) described in section 2.3.1.

Modified Silhouettes Test

The Silhouettes test forms part of a broader battery of tests called the Visual Object and Space Perception (VOSP) battery and can be used independently of the battery [29]. In its totality, the VOSP battery consists of eight tests: four tests for object perception and four tests for space perception citeSiltest. The Silhouettes test falls under the object perception half of the VOSP battery. The test consists of a number of drawings of animals and inanimate objects (generally 30 items). Each drawing differs from the others in its angle of view as well as the extent to which distinctive features can be identified. The objective is to identify and name the items. Since language can be a potential barrier, other means of identification, such as gestures or descriptions, may be used [29]. As a rule, the test should be abandoned after five consecutive failures [30].

Token Test

The Token Test assesses receptive language ability [31]. The test consists of twenty different tokens (a token refers to a distinct item) varying in shape (circle or rectangle), colour (red, green, blue, white, or yellow), and size (large or small) [32]. The objective of the test is to identify and/or manipulate the tokens based on various spoken directions. The directions are given in order of length and increasing difficulty. The original test consists of 61 commands but shortened versions of 36 commands are also used. The results of this test

reflect on factors such as short-term and working memory, language syntax and semantic development, amongst others [31].

2.2.4 Neuropsychological Test Performance

Persons with ADHD are expected to perform poorly in neuropsychological tests compared to those without ADHD [33]. This speculation is supported by a study wherein the performance of ADHD subjects was assessed relative to published norms [33]. In the study, clinical data were collected for 78 children with ADHD, where the mean age was 11 years and 10 months. The children had all been referred for neuropsychological treatment at hospitals in Texas. Inclusion criteria was age (6 to 17.9 years old) and intelligent quotient (IQ) higher than 70. All the children had been diagnosed based on DSM-4 criteria by a clinical neuropsychologist.

During the study, 36% of participants were on stimulant medications, 35% were on antianxiety or antidepressant medication, 9% were on mood stabilizers and 4% were on antipsychotics. Despite the present comorbid disorders, the study showed that it did not affect the performance of the subjects. WISC-III estimates were available for 62 of the children in the sample where the mean IQ was within average range of 91.79. Using single-sample two-tailed t tests, the sample's mean was significantly below the population mean (t -score). The following seven types of tests were done during the study: 1. attention span, 2. sustained attention, 3. single-trial learning, 4. learning with repetition, 5. retention of learning, 6. response inhibition, and 7. working memory.

Each test categories consisted of various tests. Only the overall results will be discussed. The attention span test consisted of the MAE Token Test which measures language comprehension, attention span and auditory processing. Mean performance of the sample was at the 15th percentile relative to the population performance. Fail rates for the attention span tests were between 9 and 38%. The sustained attention test made use of a VCPT test that measured the number of omissions and reaction time (RT). It was found that for emission errors, the sample performed more than 3 standard deviations below the normative mean. In contrast, reaction time was close to the normative mean. The fail rate for the omissions was 42% while that of the reaction time was 17%. As far as the other tests go, similar trends were observed in the performance. The sample score usually ranged between one to three standard deviations lower than the normative mean. The fail rate was seen to range between 10-50%. The reason for the wide range in fail rate was due to the fact that for each test, a different sample size was used.

Hence, the afore-mentioned study supports the hypothesis that persons with ADHD are expected to perform poorly compared to persons without ADHD. The study showed that there were statistically significant weaknesses

among the ADHD sample on a range of tests, compared to the norm. Academic performance was also generally observed as being near and below the mean. Furthermore, the study revealed that out of all the tests, CPT tests were the most sensitive to the weaknesses in ADHD patients.

2.2.5 Comorbidity

When evaluating a person for ADHD, it is important to assess comorbidity. Comorbidity refers to the presence of one or more additional disorder that co-occurs with a primary disorder. The implication of the comorbid nature of ADHD is that the complexity of diagnosis increases because other possible disorders have to be accounted for. Some examples of conditions that are comorbid with ADHD include: sleep disorder, learning disability, conduct disorder, anxiety, depression, sleep problems, ASD, hearing problems, epilepsy/seizures, Tourette's, eating disturbances anger/violence, vision problems, suicidal thoughts and ODD.

2.2.6 Current Diagnostic Process in South Africa

An important aspect of the diagnosis is the clinical interview with parents, the child, and other significant members in the child's life. This is necessary since the child might not be able to report symptoms accurately as opposed to a parent or teacher who has had an opportunity to observe the child. The current overall process used to evaluate and diagnose ADHD in South African schoolchildren is shown in Figure 2.5 [2] (page 16). The process begins with the identification of suspected signs and symptoms of ADHD made by either school personnel, parents or the schoolchildren themselves. These signs and symptoms may vary from being behavioural, such as anger, aggression and low self-esteem for example, to physical, such as hyperactivity and being messy.

Once signs and symptoms have been identified, the clinical process begins, wherein the full medical history is compiled. This includes physical examinations and neurological and neuropsychological examinations. The DSM-5 criteria are then assessed based on the medical history, as well as the suspected signs and symptoms. For the case where the criteria aren't met, re-evaluation is done to determine a proper diagnosis. On the other hand, when the criteria are met, comorbidities are checked for to determine whether ADHD is the primary condition or if there are other conditions present. In the case of the absence of comorbidities, the diagnosis is that ADHD is the primary chronic disorder. When comorbidities are present, however, the treatment is individualised based on the most problematic symptom.

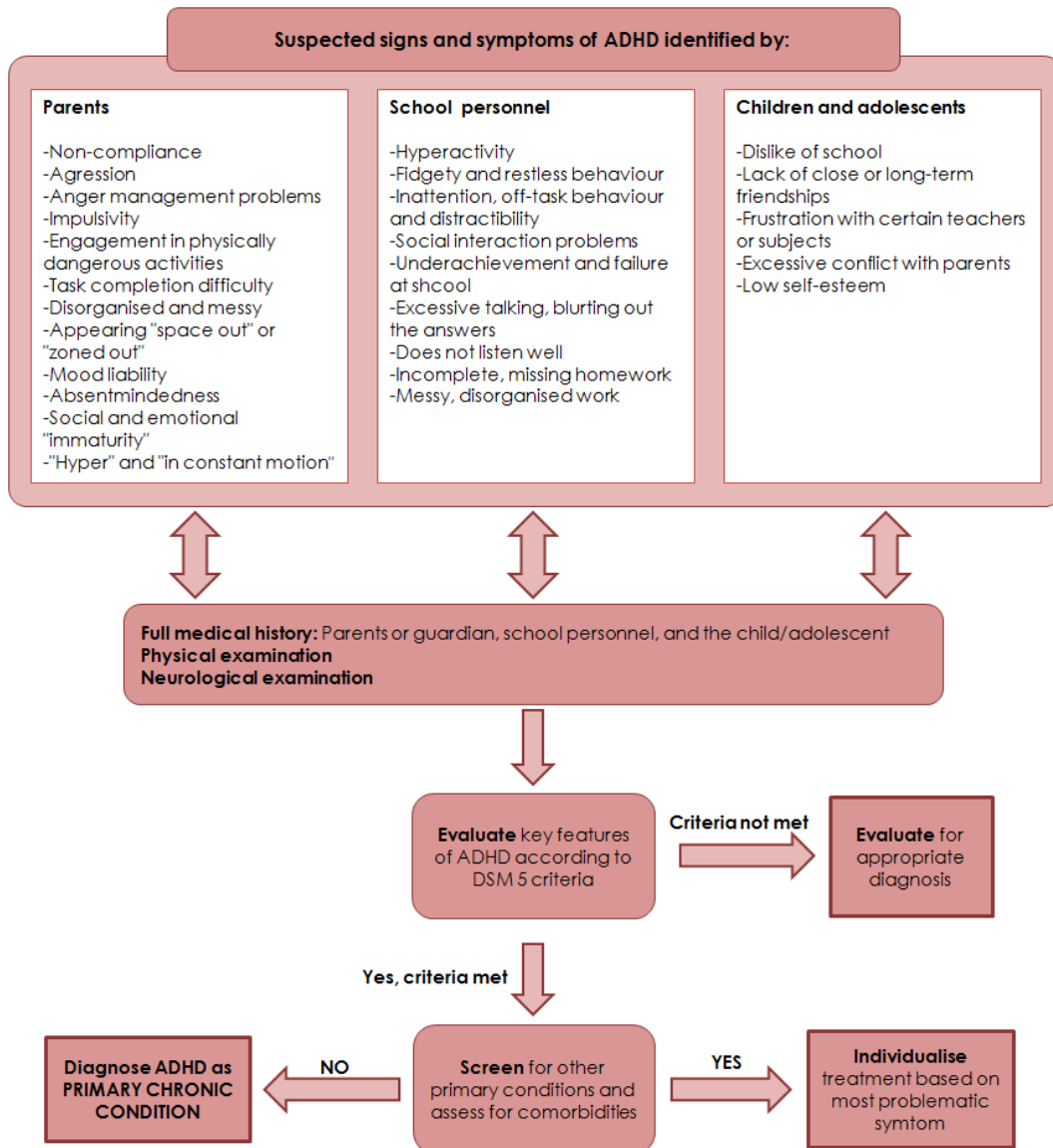


Figure 2.5: Evaluation and Diagnosis of ADHD

2.3 Existing Computerized Tools

2.3.1 Conners CPT 3

The Conners Continuous Performance Test (CPT) 3rd edition is a computerized assessment that evaluates attention disorders and neurological functioning. Its aim is to provide an objective evaluation of individuals aged eight years and older. During the 14 minute-long assessment, subjects are to click whenever any letter except 'X' appears on the screen. The four indexes that are looked at are inattentiveness, impulsivity, sustained attention, and vigilance, as explained in Table 2.2. Based on the descriptions of the indices in Table 2.2, it can be suggested that the CPT 3 Test is more prone to pick

up inattentiveness since there are five score areas for this index, as opposed to the other indices that only have three score areas. Furthermore, it is seen that omission, commission and hit response time (HRT) are used in each index.

The normative sample that was used consisted of 1400 subjects representative of the United States population in terms of demographic factors such as gender, race, geographical region and parental education level. Furthermore, the gender distribution in the normative sample was at a ratio of 1:1. The two main age groups that the sample consisted of was the 8 to 17 years old group and the 18+ years old group.

Table 2.2: Areas of Attention Measured during the CPT 3 Test

Dimension	Score	Description
Inattentiveness	Detectability (d')	Discriminating between targets and non-targets
	Omissions	Missed targets
	Commissions	Incorrect response to non-targets
	HRT ^a	Response speed
	HRT SD ^b	Response speed consistency
	Variability	Variability of response speed consistency
Impulsivity	HRT	Response speed
	Commissions	Incorrect response to non-targets
	Preservations	Random anticipatory responses (i.e. HRT < 100 ms)
Sustained attention	HRT Block Change	Change in response speed across block of trials
	Omissions by Block	Missed targets by block
	Commissions by Block	Incorrect response to non-targets by block
Vigilance	HRT ISI ^c	Change in response speed at various ISIs
	Omissions by ISI	Missed targets by ISI
	Commissions by ISI	Incorrect responses to non-targets by ISI

a: HRT = hit response time, b: SD = standard deviation, c: ISI = inter-stimulus interval

Reliability

Test-retest reliability gives an indication on the consistency of the scores obtained from a specific subject over a period of time. The CPT 3 test was administered twice to a sample of 120 subjects from the general population within a 1 to 5 week interval between the tests. The median test-retest correlation was 0.67 and this suggests good test-retest reliability.

Internal consistency was the other parameter that was measured to determine the reliability of the CPT 3 test. Split-half reliability was used as an indication of internal consistency. The median split-half reliability was 0.92 for the normative sample and 0.94 for the clinical sample. This shows that the CPT 3 test has very good internal consistency.

Validity

The validity of the Conners CPT 3 test could be shown when its results were combined with that of other similar tests/assessments of attention. In the first instance, this was demonstrated by taking the Conners CPT 3 results of a sample of 112 non-ADHD and ADHD children under the age of 18 years old. For the same sample, the results of the Conners 3rd edition parents' rating scale (Conners 3-P) were also collected. In the second instance, a sample of 137 non-ADHD and ADHD adults was taken. Their Conners Adult ADHD Rating Scales (CAARS) self-report results were combined with their Conners CPT 3 results. Logistic regressions were used to determine the accuracy of the following 3 parameters for the rating scales:

- (i) Overall classification accuracy: the ability to classify subjects correctly as either ADHD or non-ADHD;
- (ii) Sensitivity: the ability to correctly detect ADHD subjects;
- (iii) Specificity: the ability to correctly detect non-ADHD subjects.

Additionally, these same parameters were also determined when the Conners CPT 3 was used together with the Conners 3-P results and when the Conners CPT 3 was used together with CAARS. It was seen that when the CPT 3 test was used together with rating scales, the classification, sensitivity and specificity both increased notably, as seen in Table 2.3. It can be seen that the Conners 3-P report performed acceptably in terms of the three parameters. However, when used together with the CPT 3 test, the overall classification increased by 4.5 %, the sensitivity by 3.5% and the specificity by 6.3 %. The CAARS result showed that the sensitivity performed quite poorly compared to the specificity of 94.6 % and the overall classification accuracy of 89.1 %. When combined with Conners CPT 3, the sensitivity increased by just below 10 % and the overall classification accuracy and specificity both increased by 3.6 % and 2.7 %.

Table 2.3: Classification Accuracy, Sensitivity and Specificity of Conners Tests

Parameter	Conners 3-P	Conners 3-P & Conners CPT 3	CAARS	CAARS & Conners CPT 3
Accuracy	0.839	0.884	0.891	0.927
Sensitivity	0.860	0.895	0.654	0.731
Specificity	0.810	0.873	0.946	0.973

2.3.2 MOXO

MOXO Analytiscis is an innovative, online, science-based and clinically validated system [34]. MOXO provides age adjusted CPT tests accompanied with a detailed patient attentiveness profile. The test is based on the Conners CPT 3 Test in the sense that the overall task to be completed is the same. That is, to respond to a specific visual stimulus. During the computerized test the patient is required to press the space-bar on the computer's keyboard every time a specific shape/object appears on the screen while visual and auditory distractions are present. A screen-shot of a demo can be seen in Figure 2.6 [34].

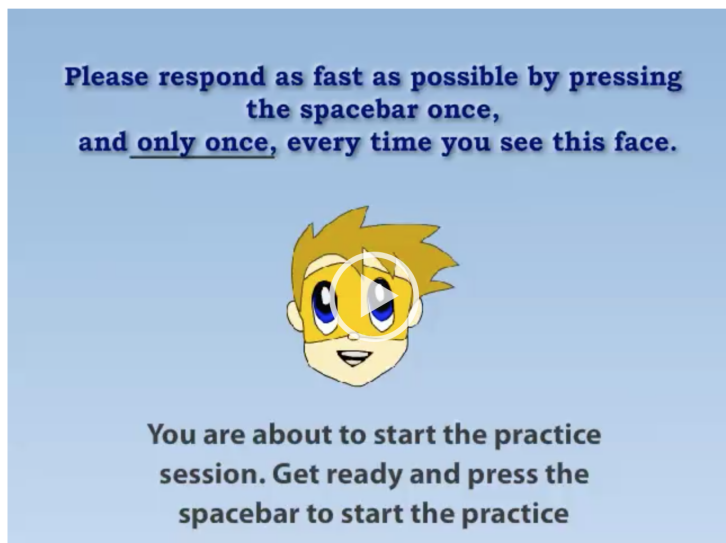


Figure 2.6: MOXO demonstration [33]

The test can only be administered by a qualified professional. MOXO provides a test for children between the age of 7 and 12 years old and for individuals between 13 and 60 years old. The children's test is 15 minutes in duration while the adult test is 18 minutes. For both test versions 8 difficulty levels are present. The following four indices are measured during the tests

and evaluated against the patient's age and gender-specific norm group: 1. Attention, 2. Timing, 3. Impulsiveness and 4. Hyperactivity.

The results of the test are presented graphically in the form of an attentiveness profile and a performance graph. Figure 2.7 [34] shows an example of an attentiveness profile. The four indices are represented by the four capital letters in the table. The examinee type describes the profile of the examinee in terms of the indices. The number that appears next to each letter is the index of performance level (1 to 4) determined by the standard z-score as described in Table 2.4 [34].

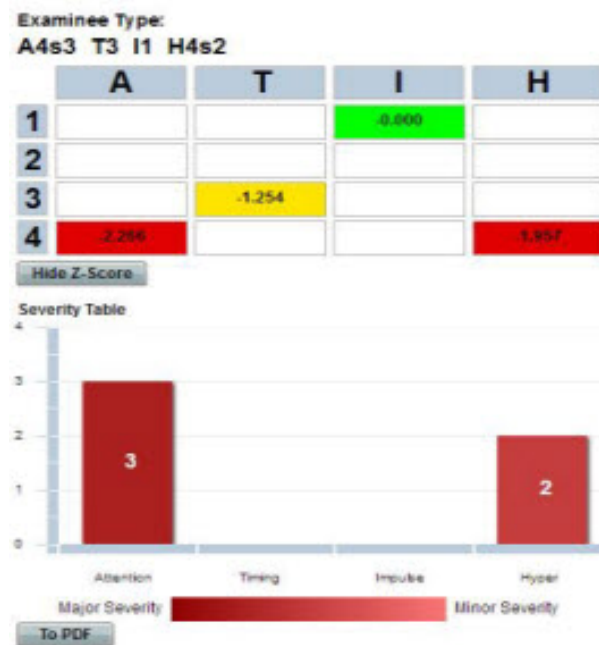


Figure 2.7: Attentiveness Profile [33]

Finally the severity index, s (1 to 4), indicates performance outside the norm range determined by the standard z-score as described in Table 2.5 [34]. The severity index does not appear when the standard score is within norm range. The matrix that appears below the Examinee Type description in Figure 2.7 graphically shows the index of performance of each attention index. The criteria table in Table 2.4 summarise this.

The last element of the attentiveness profile as seen in Figure 2.7 is the severity table. As was explained, severity indicates performance that is outside the norm range. Table 2.5 shows the severity table that describes the severity of performance impairment.

Table 2.4: MOXO Criteria Table





Level	Colour	z-score	Description
1		$Z \geq 0$	Good performance, with higher norm range (average and above)
2		$-0.825 \leq Z < 0$	Standard performance, with middle norm range (below average)
3		$-1.65 < Z \leq -0.825$	Weak performance, within low norm range
4		$-1.65 \geq Z$	Difficulty in performance, outside norm range

Table 2.5: MOXO Severity Table

Level	Severity	Position in population
1	Low	$-1.95 < Z \leq -1.65$ (2% of population)
2	Medium	$-2.25 < Z \leq -1.95$ (1.5% of population)
3	High	$-2.55 < Z \leq -2.25$ (0.75% of population)
4	Extreme	$-2.75 < Z \leq -2.55$ (0.75% of population)

For example, for the Examinee Type “A4s3 T3 I1 H4s2” shown in the top left of Figure 2.7, the interpretation of the attentiveness profile type is as follows:

1. Attention performance index is 4 with high severity, outside the norm range;
2. Timing performance index is 3, within the low-norm range;
3. Impulsivity performance index is 1, within the higher-norm range;
4. Hyperactivity performance index is 4 with medium severity, outside the norm range

As previously mentioned, the other graphical representation of the results is presented in the form of a performance graph. This graph shows the performance score (0 to 100) for each index (attention, timing, impulsivity and hyperactivity) on the y-axis vs the different game levels on the x-axis. It must be noted that the performance score is a reflection of the number of key presses and not based on the average score in the sample. In determining the performance score for the attention and timing indices, the more key presses

represent a higher score. In contrast, for the impulsiveness and hyperactivity indices, a higher score is achieved when the key presses are kept low. A typical performance graph is shown in Figure 2.8 [34].

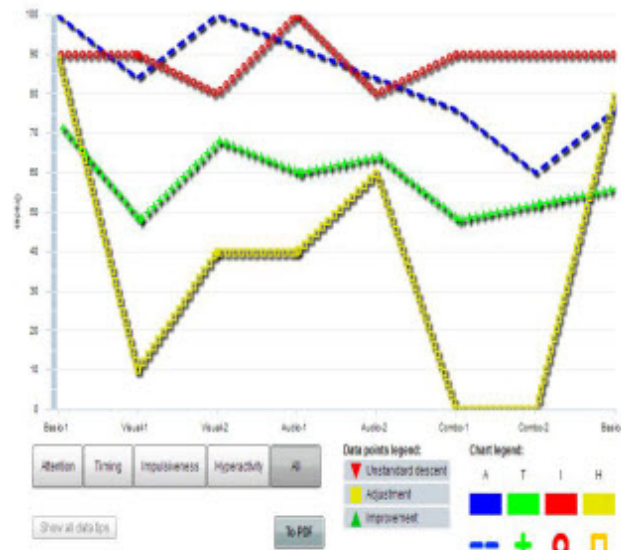


Figure 2.8: MOXO Performance Graph [33]

In this example, it can be seen the the performance for the attention index and for the time were generally stable throughout the test. The hyperactivity changed drastically between levels. This can be explained by the fact that some levels include distractors while others do not. The impulsivity, although stable, showed poor performance.

Validity of MOXO

Two studies found in literature provide evidence of the validity of the MOXO test in terms of its ability to correctly discriminate between ADHD and non-ADHD individuals. The rationale behind the studies in using MOXO was that the inclusion of the distracting auditory and visual stimuli improves the diagnosis [35].

The first study that supports the validity of the MOXO test was conducted with 663 children between 7 and 12 years old, with 345 children in the ADHD group 318 children in the non-ADHD group [36]. It was hypothesised that ADHD children would have more omission errors when pure visual, pure auditory, and a combination of both types of distracting stimuli were present. The results validated the hypothesis by showing that ADHD children committed more omission errors than their non-ADHD peers across all test conditions

Table 2.6: Omission errors between ADHD and non-ADHD Children

Level	Distractor Type	ADHD (N = 345)		Non-ADHD (N = 318)	
		M	SD	M	SD
1	Base line	1.80	2.57	0.80	1.30
2	Visual ^a	3.21	3.38	1.19	1.32
3	Visual ^b	2.73	3.09	1.18	1.42
4	Auditory ^a	2.50	3.21	0.95	1.25
5	Auditory ^b	2.74	3.86	0.97	1.39
6	Combined ^a	3.52	3.90	1.58	1.64
7	Combined ^b	3.45	4.17	1.75	2.17
8	No distractors	2.26	3.19	1.21	1.95

M = mean, SD = standard deviation, a = low distractibility, b = high distractibility

(no distracting stimuli, only auditory or visual stimuli, combined distracting stimuli) and all levels. Furthermore, the results showed that for non-ADHD children, the omission errors only increased when combined distractors were used while for ADHD, the omission errors increased for all types of distracting stimuli. The detailed results of the study are shown in Table 2.6 [36].

As can be seen from Table 2.6, the means and standard deviations for each distractor type are smaller by approximately a factor of 0.5 for the non-ADHD group compared to the ADHD group. For both groups the combined distractor with high distractibility gave the highest omission errors (4.17 SD for the ADHD group and 2.17 SD for the non-ADHD group). The baseline distractor type gave the smallest omission errors (2.57 SD for the ADHD group and 1.3 SD for the non-ADHD group). Based on these results, it can be suggested that MOXO can discriminate between an ADHD group and a non-ADHD group where the feature with the highest discrimination ability is the combined distractor with high distractibility.

The second study aimed to show that the MOXO adult's test could correctly classify ADHD and non-ADHD teenagers. Adolescent ADHD is of interest because it is more complex to pick up compared to childhood ADHD. This is due to the fact that ADHD in adolescents and adults is accompanied with various comorbidities [37]. The study analysed the performance of 176 adolescents between 13 and 18 years old on the MOXO test. The ADHD group consisted of 133 adolescents while the non-ADHD group was 43 adolescents. Similar to the two previous studies, the hypothesis was that ADHD adolescents would perform more poorly than their non-ADHD peers in the presence of distracting stimuli. The detailed results of the study are shown in Table 2.7 [35].

The results show that ADHD adolescents have more omission errors than their

Table 2.7: Omission errors between ADHD and non-ADHD Adolescents

Distractor Type	ADHD (N = 143)		Non-ADHD (N = 33)	
	M	SD	M	SD
No distractors	2.17	0.44	0.58	1.22
Visual distractors	3.56	3.24	1.02	2.09
Auditory distractors	2.46	2.95	0.81	2.14
Combined distractors	3.92	3.49	0.88	2.45

M = mean, SD = standard deviation

non-ADHD peers. This can be seen by the mean values for the ADHD group being almost double that of the non-ADHD group. Similar to the previous study, the omission error is higher for the combined stimulus (3.49 SD for the ADHD group and 2.45 SD for the non-ADHD group). Finally, the lowest omission errors occurred in the absence of distractors (0.44 SD for the ADHD group and 1.22 SD for the non-ADHD group). The same conclusion can be drawn as for the previous study. The MOXO test can be used to discriminate between ADHD adolescents and non-ADHD ones. Once more, the feature with the highest discriminatory ability was the combined distractor.

2.4 Existing Sensor-Based Tools

So far, only computerized tests and software tools have been discussed as solutions to diagnose ADHD. However, literature shows that hardware can also be used to give an indication of the presence of ADHD. This hardware is mainly in the form of sensors. The rest of the discussion will focus on two types of sensor-based tools. The first tool is inertial measurement units (IMUs) and the second is electroencephalography.

2.4.1 Objective Diagnosis of ADHD using IMUs

A study was conducted wherein miniature wireless inertial sensors were used as an objective tool for diagnosing ADHD [38]. The rationale behind the use of IMUs is that they can accurately measure linear and rotational movement using accelerometers and gyroscopes. The measured data can then be used together with sophisticated data analysis methods such as machine learning, to develop a typical statistical profile that characterises an ADHD individual and a non-ADHD individual.

The subjects were 43 children between the ages of 6 and 11 years who were referred to the Child and Adolescent Psychiatry Unit of the Department of Psychiatry at Fundación Jiménez Díaz Hospital in Madrid, Spain. The experimental group consisted of the children diagnosed with ADHD (N = 24)

while the control group consisted of those that did not meet DSM 5 criteria for ADHD ($N = 19$).

The procedure that was used to record data for each subject was to attach one IMU to the subject's belt (located at the waist) and another IMU was fixed to the ankle of the subject's dominant foot using a velcro strap. The reason for having two IMUs was that the one attached to the belt would give global measurements of the body while the one on the ankle would capture local movement. The two IMUs were attached to the subjects during their hour-long visit to the psychiatric consultancy. The subjects were put into five different contexts during their visit. In this study, the term "context" referred to the "where, what and with whom" of the subject's environment [38]. The five contexts are shown in Table 2.8 [38]

Table 2.8: Contexts Used for Diagnosing ADHD with IMUs

Label	Context Description
WP	Waiting room; with parents
WS	Waiting room; with supervisor only
CD	Consultant's room; with psychiatrist
CP	Consultant's room; with psychiatrist and parents
TT	Taking the TOVA test; with supervisor only

The machine learning method that was used was a support vector machine with a linear kernel. The most representative feature set was calculated for the gyroscope and the accelerometer, for each sensor location and for each context. Age, gender and T.O.V.A score were also used as features. The following feature categories were used, where the number of features is shown in brackets: 1. high resolution histograms (35), 2. correlation between sensors/sensor types (8), 3. basic statistics (52), 4. frequency domain (8), 5. nonlinear features (4), 6. structural features (20), 7. motion features (6), 8. total per context (133) and 9. test of variables of attention (TOVA) score, age, gender (3). This resulted in a total of 688 features. Furthermore, a forward-selection method was used to select the features that achieved the best classification accuracy in each context. This resulted in a maximum of 15 features per context.

Table 2.9 [38] shows the classification performance of each context, as well as specificity and sensitivity. It can be seen that the overall accuracy of the SVM is good, where the lowest accuracy was 81.40%. Specificity and sensitivity were satisfactory, although sensitivity was generally lower: the minimum sensitivity was 73.68% while the minimum specificity was 81.81%. The results show that the best classification performance was achieved when all contexts

Table 2.9: Classification Performance of SVM for Diagnosing ADHD with IMUs

Context	k	Accuracy	Sensitivity	Specificity
WP	5	0.8372	0.7368	0.9167
WS	14	0.8537	0.8947	0.8181
CD	7	0.8372	0.7368	0.9167
CP	5	0.8140	0.5789	1
TT	6	0.9302	0.8947	0.9583
All	10	0.9512	0.9444	0.9565

were combined. The reported accuracy for this setting was 95.12%, the sensitivity was 94.44%, and the specificity was 95.65%. It was seen that the most accurate results in discriminating between ADHD and non-ADHD, other than the combined contexts, occurred when concentration was required. In this setting, the reported accuracy, sensitivity and specificity were reported as 93.02%, 89.47% and 94.83% respectively. Furthermore, it was seen that the IMU that measured global movement provided better discrimination than the one that measured locally [38].

2.4.2 ADHD Diagnosis with EEG

NEBA is the first FDA-approved medical device that uses EEG to help clinicians to more accurately diagnose ADHD in children between the ages of 6 and 17 years [39]. The device measures the electrical activity in the front part of the brain and this allows clinicians to determine whether the symptoms are due to ADHD or some comorbid disorder. The duration of the test is approximately 20 minutes. One of the greatest challenges with the device is its cost. Some specialists have questioned whether the device would be any better than current diagnoses [40].

The most recent study spread over 13 independent sites and included 275 children presenting signs and symptoms of ADHD [41]. Their full clinical evaluation data was used in conjunction with the EEG data. Qualified clinicians were used to perform differential diagnosis, while a separate team performed the EEG tests and collected data. The gold standard used was consensus diagnosis by a multidisciplinary team.

The results showed that out of the 209 children that were clinically diagnosed as per site, 93 of them were overdiagnosed by the multidisciplinary team. Furthermore, 85 of the 93 children were also identified by EEG. Ultimately, it was seen that the integration of EEG with the consensus diagnosis yielded

a 97% accuracy. In conclusion, the results showed that the EEG integration may help reduce overdiagnosis.

2.5 Summary of Literature

Literature was reviewed using searches on two databases: Stellenbosch University Library Database and Mendeley. For the former database, the advanced search option was chosen to narrow the searches to specific hits. The scope of the literature reviewed was limited to the following categories: aetiology, diagnosis, treatment and existing methods. The year of publication was generally kept between 2005 and the current year. In some cases, older papers were the most relevant ones or were referred to in other papers and were therefore included in the review.

The method that was used was to search for articles and papers that included the term "ADHD" in the title. To refine the searches, different combinations of the following keywords were added to the main term: aetiology, causes, risk factor, genetic factor, prevalence, worldwide, gender, treatment, drugs, overdiagnosis, diagnosis, objective, computerised, neurophysiological, software, machine learning, validity, sensitivity, specificity. The papers that were reviewed were the ones that were most relevant in both databases in terms of citations. In total, 30 articles were reviewed. Additionally, some information was obtained directly from websites such as the online-based tools like MOXO and.

The research community and specialists accept that the origin and cause of ADHD are both unknown [2; 7; 8; 9]. However, studies support the likelihood of genetic inheritance and heritability of the disorder [7; 9; 11]. It is also seen that environmental factors such as psychosocial and peri/pre-natal factors contribute to the development of ADHD although such factors may be consequential rather than causal [2; 10]. In terms of its neurobiology, it is widely accepted that ADHD is associated with dysfunction of the prefrontal cortex [7; 19; 20].

Diagnosis of ADHD is based on clinical criteria defined by DSM 5 (or ICD 10 for Europe) [2]. Proper diagnosis involves clinical interviews with the child and parents, psychometric testing (in South Africa the JSAIS test battery is often used) and rating scales completed by parents/guardian, teachers and the specialist [8; 23]. Since comorbidity is likely to occur, diagnosis must be treated as being patient-specific. Although data on prevalence in South Africa is incomplete, it is generally considered to be similar for youth worldwide, between 4 – 10 % [42; 43].

Literature strongly shows that there is a need to develop objective tools for ADHD diagnosis. The method with the most accurate discriminatory ability was found to be CPT testing with environmental distractors [35; 44; 36]. MOXO is an example of a tool that uses this method [34]. Although it is a good baseline tool for discriminating between ADHD and non-ADHD, it does not include any form of cognitive testing and might therefore fail to discriminate between different subtypes of the disorder. Another study showed that an objective ADHD diagnosis can be made using inertial sensors attached to a subject [38]. Currently, there exists another FDA-approved device called NEBA. It uses EEG signals to aid the clinician when making a diagnosis [39].

In conclusion, the literature reveals that there are increasing efforts in developing objective tools. However, although there may be many tools available, very few, except for MOXO, have been validated in terms of specificity and sensitivity. Furthermore, no tool exists that uses an interactive market-place game. Instead, most tools use CPT tasks and computerized neuropsychological tests.

Chapter 3

Design Specification

A detailed description of the design process is given in the following chapter. The importance of the design specification is that it transforms the user requirements into a prototype that meets the overall objectives of the study. As discussed in the introductory chapter, the proposed method for achieving the objectives was a multi-layered software tool. The top layer was the game and user interface while the underlying layers consisted of data gathering tools, data-processing, and machine learning algorithms. This chapter will give a detailed specification of each of the different layers of the software tool. As such, each section of the chapter will deal with one of the layers. Since the development of the game was not the direct outcome of this research, it was outsourced to a gaming developer. The role of the developer was to create the back and front ends of the game. The back end dealt with the functionality of the game from a programming perspective while the front end allowed for pre-constructed building blocks such as tiles and items to be drag-and-dropped to create the gaming environment. In this way, the researchers had freedom of design in terms of the layout of the environment.

3.1 Game Development

While the literature presented various traditional methods for diagnosing ADHD, the chosen approach for designing the software tool was to develop a game that was easy to play, without necessarily including some of the aspects of the traditional methods. The development of the game began with translating DSM-5 criteria into measurable parameters. Thereafter, possible game mechanics were investigated. In this context the term “game mechanic” refers to how the user interacts with the game itself (e.g. pressing a button to initiate an action vs using voice commands to initiate an action), as well as how the objects and characters within the game environment interact with each other (e.g. 2D vs 3D, range of motion of characters, etc.) The following step was to determine a game theme, a game task and a simple storyline with characters. The development sequence that was followed can be seen in Figure 3.1. The output

of the sequence was a game, ready to be deployed on a device.

3.1.1 Measurable Parameters from DSM-V

DSM-5 criteria for ADHD were analysed with the aim being to translate them into measurable parameters. It was seen that not all criteria could be translated into quantifiable parameters. This was especially true with the criteria for the hyperactivity subtype. Since the game was a screening tool, not all the criteria had to be quantified. The resulting parameters are given in Table 3.1. The parameter names are given in the first column. As will be explained subsequently, each parameter has one or more variables associated to it. The value of the variables is what is ultimately stored at the end of game-play. The relevant DSM-5 criteria can be read from Table 3.2. The third column gives the units that the variable(s) associated to each parameters is in. Finally, the last column gives a brief description of the parameter.

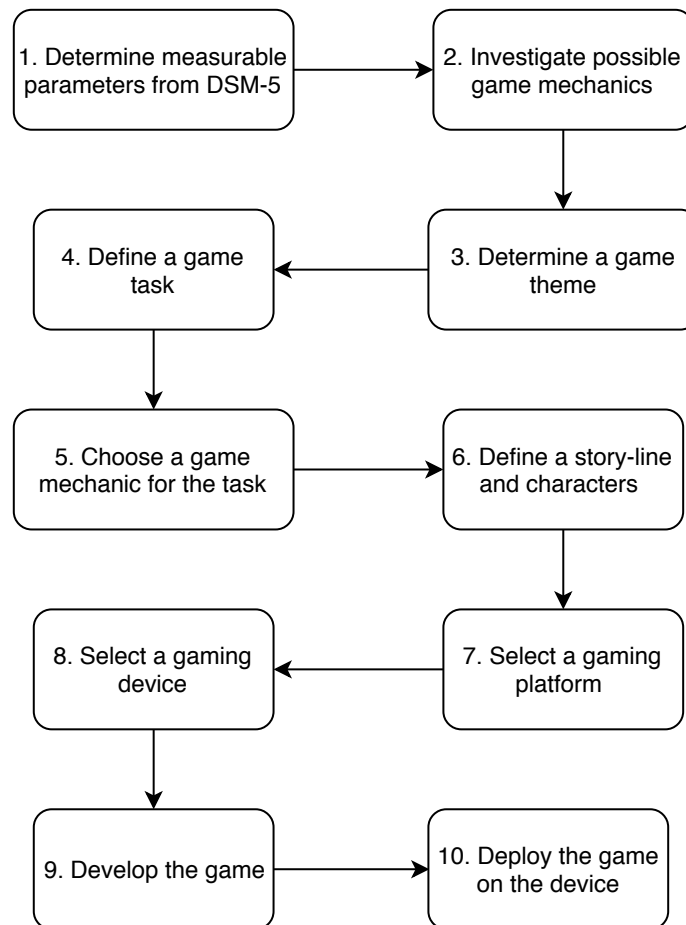


Figure 3.1: Game Development Sequence

Table 3.1: Measurable Parameters

Parameter	DSM 5 Criteria	Units	Description
Mistakes made	A,B,C,E	number of occurrences	The total number of mistakes made during a task
Task completion time	A,B,C,D,E	<i>s</i>	The amount of time taken to complete a task
Task termination	D	yes/no	Whether or not the user quit a task before completing it
Distractibility	B,E	number of occurrences	The number of distractions that affected the user's performance in a task
Forgetfulness	F	yes/no	The user's ability to remember an item/feature
Sustained attention	B	<i>s</i>	The amount of time the user can focus on a specific feature
Device motion	G, I	<i>m.s⁻²</i>	Data from the device's accelerometer and gyroscope

Table 3.2: Labels given to Relevant DSM 5 Criteria

A	Little attention given to detail
B	Difficulty keeping sustained attention
C	Failure to follow through on instructions
D	Avoidance of tasks that require sustained mental attention
E	Distracted easily by external stimuli
F	Forgetfulness with regards to daily activities
G	Constant fidgety behaviour
H	Inability to quietly engage in leisure activities
I	Constantly active and "on the go"

3.1.2 Development Platform and Device Selection

Various gaming platforms can be used to develop games. The selection was narrowed down to two choices: Unreal Engine and Unity. Based on the gaming developer's preference, Unreal Engine 4.18 was chosen. Ultimately, both these platforms are very well suited for development and deployment on various devices on different operating systems such as Android and iOS. As mentioned

previously, since the gaming development was outsourced, given a clear design specification, the choice of development platform was left to the developer. One of the benefits of using a dedicated gaming platform such as Unreal Engine is its online marketplace. The marketplace gives developers access to a wide range of packages called assets. Assets are items that are used to build the gaming environment. Furthermore, the marketplace categorises assets based on their theme. Therefore, the use of assets reduces the amount of development.

Similar to selecting a suitable development platform for the game, the selection of a gaming device was recommended by the gaming developer. As a result, the device that was selected for the study was the NVIDIA K1 Shield tablet (see Appendix x for technical specifications). The K1 Shield is a specialised gaming tablet with optimal processing and graphical performance. It was chosen as the testing device to eliminate the risk of hardware limitations (e.g. low processing and low memory for example) that may have occurred with other devices. This allowed for greater freedom in the actual software design itself. Additionally, the smaller size of the tablet (221 x 126 x 9.2 mm), compared to most standard tablets, meant that it could be held with two hands by minors, whose hands may be too small to firmly hold a large tablet.

3.1.3 Game Theme

The theme that was chosen took into account the age group of the subjects that were used for the research. Since the subjects were schoolchildren a jungle/tropical theme was seen as a logical choice. Furthermore, this theme was seen as being culture neutral, as all schoolchildren could relate to the theme. The character that the user interacted with was a panda bear that was created in Unreal Engine. Details such as skeletal structure, joint movements, physics and animations were implemented for the character in a process called rigging. The panda character can be seen in Figure 3.2.



Figure 3.2: Panda character

The game environment consisted of a map and disposable items. The map was used to define the path that the character followed during game-play. The building blocks of the map were pre-constructed tiles that could be drag-and-dropped in sequence. There were 9 different types of tiles that could be used, as seen in Figure 3.3. The last tile, seen on the bottom right of Figure 3.3 was the “Finish Tile” and represented the end point of the map. The disposable items consisted of obstacles that the character had to avoid, as well as collectable items or “pick-ups” that contributed to the user’s final score. The types of obstacles that were present can be seen in Figure 3.4 while Figure 3.5 shows a small portion of the map, consisting of tiles in succession as well as disposable items.

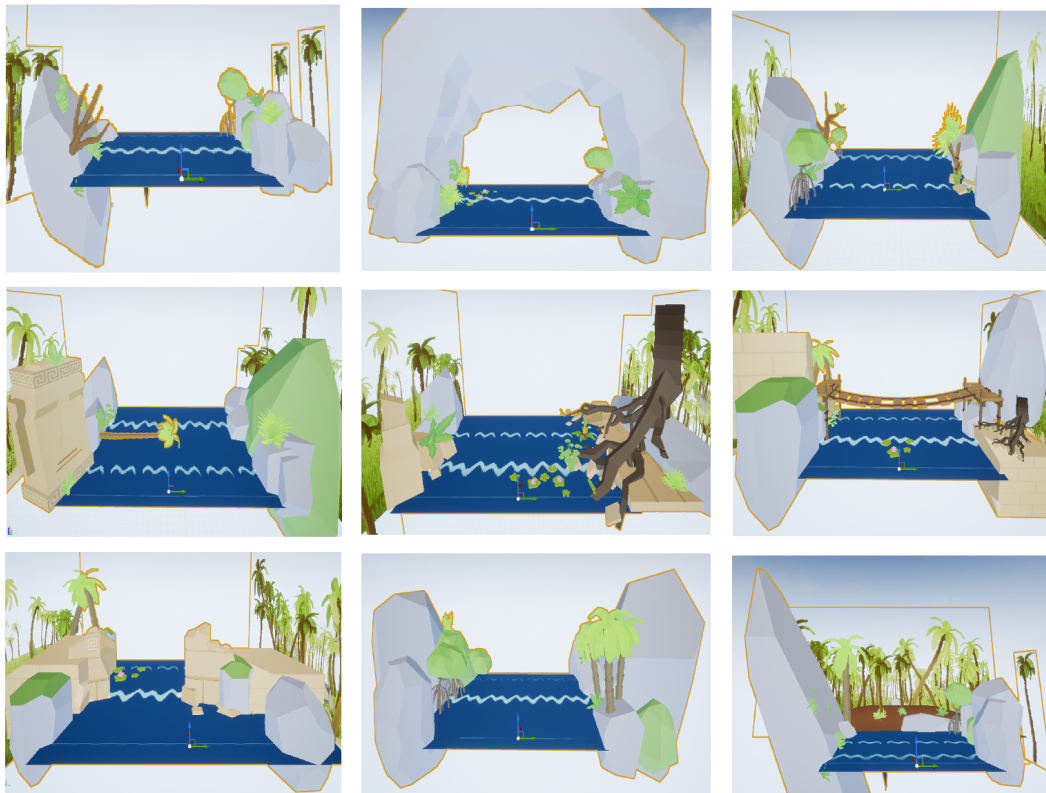


Figure 3.3: Tiles for Creating a Map

3.1.4 Game Task Description

The objective of the task was to travel on a raft from one end of a river to the other end as quickly as possible. This had to be done while avoiding obstacles and collecting as many gems as possible. The speed of the raft increased as the game progressed, provided that no obstacles were hit. Three straight lanes were present and the user was able to move to the left or right lane, while the

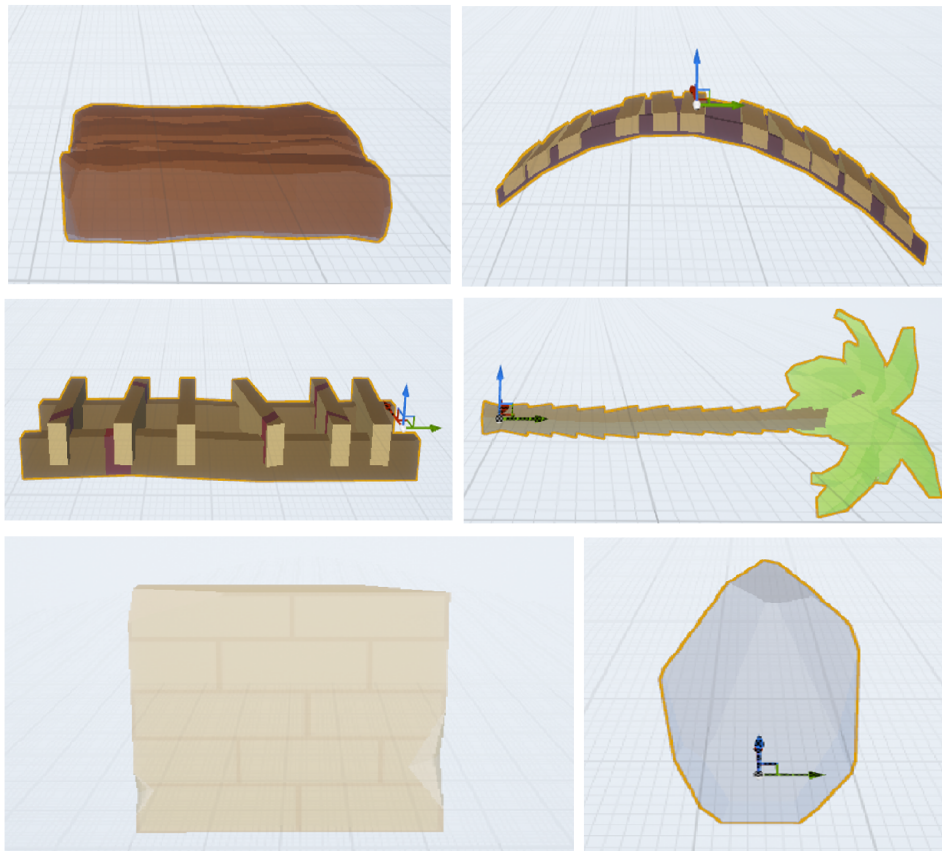


Figure 3.4: Disposable Items – Obstacles

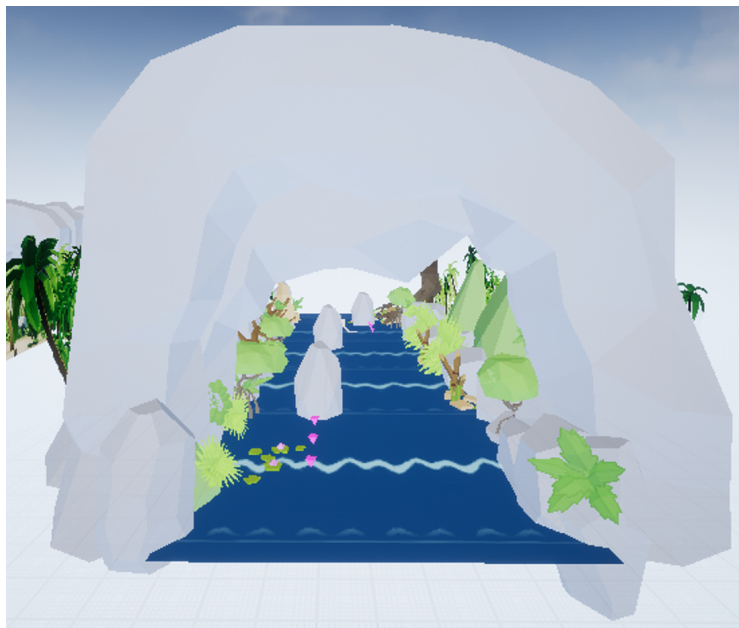


Figure 3.5: Map Example

middle lane was the default lane. The main game window can be seen in Figure 3.6. The top left corner displays the number of gems collected and the top right corner has two buttons. The button marked with the letter “M” allowed the user to go to a welcome page while the button marked with “X” allowed the user to terminate the game. The red buttons at the bottom of the screen were used to navigate along the lanes of the river and avoid incoming obstacles. The obstacles could be avoided by switching lanes, jumping over them, or throwing a rock in their direction (the throw and jump buttons are labelled “THROW BTN” and “JUMP BTN” respectively). These moves are explained in more detail subsequently. The user was able to control the character and make the moves discussed previously by means of the following four button commands: left button command, right button command, jump button command and throw button command.



Figure 3.6: Main Game Window

An important feature of game-play was respawning. This occurred every time the character collided with an obstacle. Figure 3.7 shows a scenario where the character was approaching an obstacle. The respawn location was always located near the obstacle where collision occurred. The principle was that the game would resume only 5 seconds after respawning. A notification message as well as a 5 second timer appeared on the screen. Upon resuming, the character’s speed would start from rest and begin to increase gradually. Therefore, the more obstacles collided with, the longer the duration of the game. and Figure 3.8 shows the respawning action that occurs after collision with that obstacle.

As explained previously, the gaming device that was chosen was a NVIDIA K1 Shield tablet. Its convenient dimensions made it easy for children to hold



Figure 3.7: Scenario 1 – Character Approaching an Obstacle



Figure 3.8: Scenario 2 – Character Respawnng after Collision

it comfortably with both hands. The tablet was to be held in a “landscape” orientation (i.e. with each hand being on each short side of the tablet). The device had to be held in this configuration in order to get the most representative data. As seen in Figures 3.7 and 3.8, the button commands were located in such a way that when the device was held correctly, the buttons could be pressed with the thumbs of each hand.

Buttons were chosen to navigate between lanes as opposed to the gyroscope sensor of the device. The choice of using buttons was made with the

assumption that more meaningful data from the hyperactivity group would be captured if the default motion of the device was as close to still as possible. Therefore, this data was expected to deviate more from the default still motion, since the hyperactivity group tends to show more impulsive and uncontrolled movements. Another reason why buttons were preferred was that the number of button presses could be counted. As such, factors like impulsivity, aggressiveness and frustration could be quantified.

Obstacles could be avoided in three possible ways. The first way was to move to a lane away from the obstacle. For example, if the character was travelling in the middle lane and the next obstacle was in that lane, then moving to the left or right lanes would avoid collision. This scenario is illustrated in Figure 3.9 where the character moves to the left to avoid the obstacle that spans the middle and right lanes. It can be seen that the left button was pressed. Similarly, the character could move to the right lane, as seen in Figure 3.10. The main feature of the buttons is that they collapse when they are pressed.

The second possible move that could be performed to avoid obstacles was to jump over them. This is illustrated in Figure 3.11. This move could only be performed for obstacles whose heights were small enough, such as the tree logs, and the ladder. Obstacles such as the boulders and the big walls could not be jumped over due to their heights. This method added a level of complexity to the game-play since it forced players to consider obstacle height before jumping.

The last way in which obstacles could be destroyed was to throw a rock in the direction of the obstacle. The throw command worked in such a way that there was a fixed interval between when a rock was thrown and when



Figure 3.9: Scenario 3 – Character Moving to the Left Lane



Figure 3.10: Scenario 4 – Character Moving to the Right Lane

the next rock was available to be thrown. For example, if the user threw a rock, the next rock could only be thrown 5 seconds later. Obstacles could only be destroyed by throwing, provided the thrown rock made contact with that obstacle. The throw command is shown in Figure 3.12. It can be seen that when the button is pressed, a small rock is thrown away from the character. Further functionality of the buttons made it possible for the user to press two buttons simultaneously in the following combinations: moving to the left lane and throwing/jumping or moving to the right lane and throwing/jumping. Finally, when the character completed the task, a message appeared as shown



Figure 3.11: Scenario 5 – Character Jumping over Obstacle



Figure 3.12: Scenario 6 – Character Throwing a Rock at an Approaching Obstacle

in Figure 3.13.

3.2 Data Gathering, Storage and Extraction

Data gathering and storage formed part of the back-end of the software. As discussed in the previous section, data was captured in real-time during game-play by means of game variables. These variables were then stored at the end of a game session. The two tools for storing data were a FireBase database and a



Figure 3.13: Scenario 7 – Character Reaching the End of the Task

Microsoft Excel 2016 Spreadsheet. The former was used to store game variables from the back-end of the software while the latter was used for personal user data, which was manually recorded into the spreadsheet for each game session. Data gathering and storage is illustrated in Figure 3.14.

3.2.1 Data Gathering

User specific personal data was recorded and stored manually in a spreadsheet for each game session. For the study specifically, this data was not stored on the FireBase database. However, for future development of the software tool, user data input will be part of the game itself. Personal user data was stored in the following variables:

1. Age
2. Gender
3. Race
4. Game enjoyment (yes or no)
5. Diagnosis (ADHD or normal)
6. Date and time stamp

Game variables were used to store game-play data in real time. The variables were derived from the measurable parameters discussed in section 4.4. Two types of variables were defined: game-play variables and an accelerometer variables. Game-play variables were variables that were related for the types of moves that the user made. For example, number of lane switches, number of jumps and number of throws. The full list of game-play variables, is given in Table 3.3. Each variable's units, typical expected range and description are

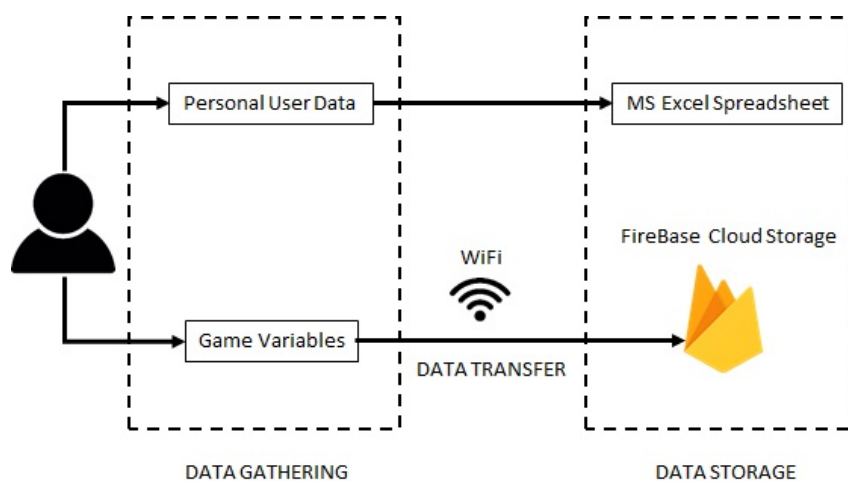


Figure 3.14: Data Gathering and Storage

given. The values shown for the range are for one game session. For instance, during one game session, the total number of obstacles present in the map is 30. Therefore, the range for the number of obstacles hit and obstacles destroyed is 0 to 30. Additionally, a unique session identifier and a time stamp were generated for each session.

On the other hand, the accelerometer variables were used to store the raw data from the accelerometer of the device. The accelerometer measured the device's acceleration in the x-plane, y-plane and z-plane. For the purpose of the software, the sampling rate for reading the accelerometer values was taken as $100Hz$. Using the value for the maximum task completion time in Table ??, number of samples recorded in each plane ranged between 12000 and 30000. The accelerometer data was useful because it could help quantify the relative motion of the device during game-play. This in turn would help to classify between non-ADHD and ADHD persons.

3.2.2 Data Storage

At the end of a game session, the game variables were sent to a FireBase database using a WiFi connection. This data transfer was automatically triggered when the user reached the end of the task. This is explained graphically

Table 3.3: List of Game-Play Variables

Variable name	Units	Range	Description
Left_cnt	# occurrences	0 – 50	number of “left” button presses
Right_cnt	# occurrences	0 – 50	number of “right” button presses
Throw_cnt	# occurrences	0 – 50	number of “throw” button presses
Jump_cnt	# occurrences	0 – 50	number of “jump” button presses
Obst_hit	# occurrences	0 – 30	number of obstacle collisions
Obst_des	# occurrences	0 – 30	number of obstacles destroyed
Gem_cnt	# occurrences	0 – 120	number of gems collected
Dur	s	120 – 300	Task completion time
Qt	binary	1 or 0	Task termination before reaching the end

in Figure 3.15. The FireBase database was password protected and could be accessed remotely. For the purposes of this study, data security was not a priority, therefore the low level of security was acceptable. The way in which the data was stored on the database was that for each session, a database entry was created. The spreadsheet entries could be linked to their associated FireBase entries by matching the time stamps.

3.2.3 Data Extraction

Individual FireBase entries could be downloaded into .json files. Basic file processing was done to extract the data from the files and store them into the appropriate structures and format for the machine learning algorithms. Figure 3.16 shows the file processing flowchart. The sequence of the data extraction began when a subject started playing the game. During game-play, data was recorded and stored into variables referred to as game variables, as shown in Table 3.3. Additionally, accelerometer data was also recorded during game-play. This recorded data was then saved in the Firebase database in the form of a .json file.

The .json file was then downloaded and based on the unique identifier in that file, the corresponding entry was found in the MS Excel spreadsheet containing all the personal user data. Two steps then occurred in parallel. The first one, dealing with the extraction of the accelerometer data, while the

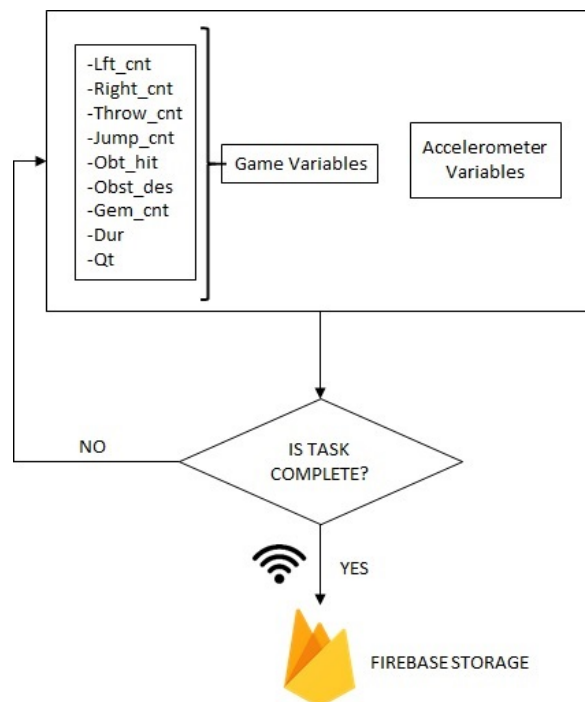


Figure 3.15: Transfer and Storage of Game Variables

second one dealt with the game-play data. A .csv file `UserGamePlay.csv` was created and contained each user's game-play variables, as well as personal data variables. `UserGamePlay.csv` was one of the two matrices used as input data to the machine learning algorithm. The dimension of the `UserGamePlay` matrix was $m \times k$, where m was the number of subjects used to train the machine learning, and k the number of variables (nine game-play variables, and four personal user data variables). The second matrix that was created was the A-matrix: an $m \times 3n$ matrix containing each user's accelerometer data. In this case n referred to the maximum number of accelerometer samples recorded during a session (22000) and $3n$ corresponded to the 3 planes x, y and z. Matrix dimensions and derivations are explained in chapter 5.

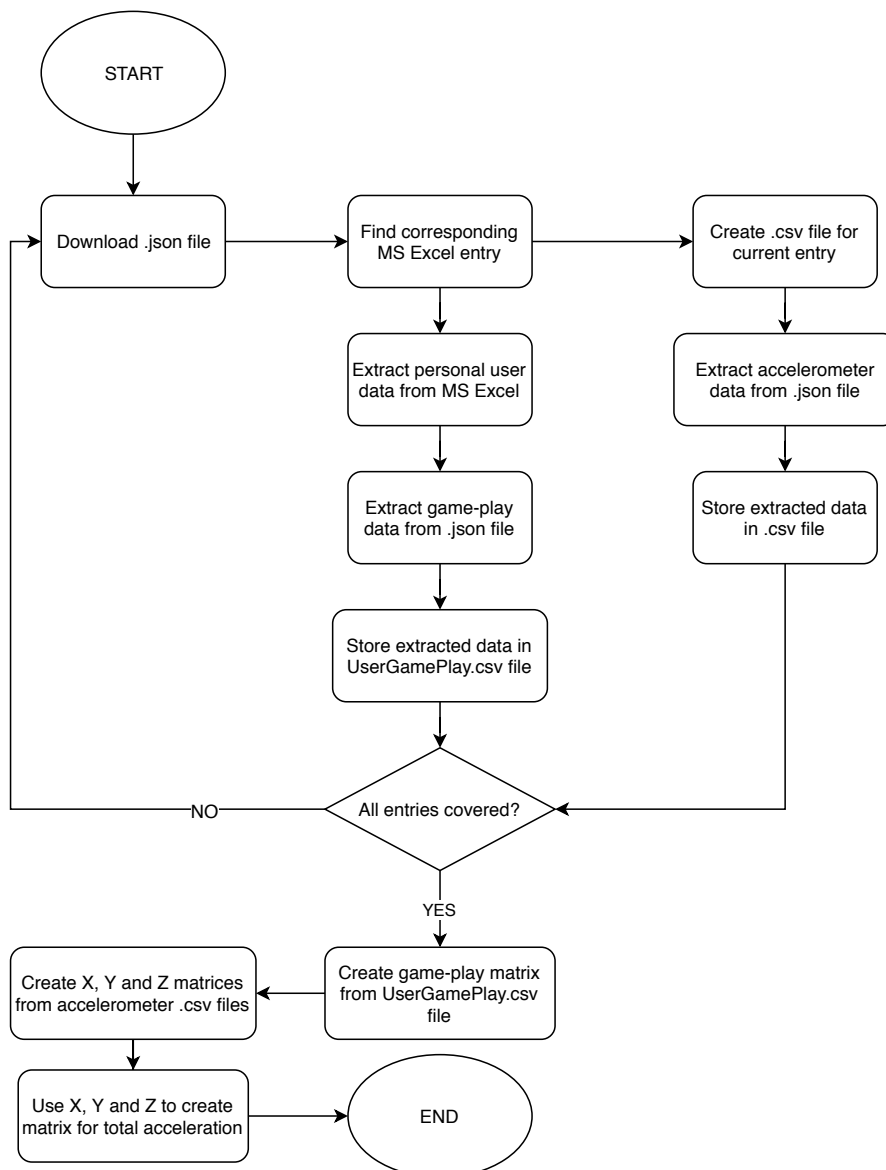


Figure 3.16: Data Extraction Flowchart

Chapter 4

Research Methodology

This chapter provides a detailed discussion of the chosen study design that answered the research question posed in chapter 1. The discussion begins with a description of the research approach, a description of the subjects and the selection method that was used. This will be followed by the ethical considerations of the study. The research protocol will then be presented. This consists of a detailed sequence of activities and procedures that were followed during the study. Next, the measurements and calculations will be discussed and this will be followed by a description of the data analysis (i.e. sample size estimations and statistical tests performed). Finally, a synthesis of the methodology will be given where possible limitations are evaluated.

4.1 Research Approach

Traditionally speaking, the diagnosis of ADHD relies on subjective and qualitative assessments. The proposed method to answer the research question was to use a quantitative approach to solve this qualitative problem. The departure point of the study was that certain parameters can be identified from some of the diagnostic criteria for ADHD and used as metrics for quantifying the presence, or lack thereof, of the disorder in a particular person. These parameters were discussed in the chapter 3. One of the main aspects of the research was to gather data through a beta-testing phase and a clinical trial phase. This data was then used to develop a machine learning model. The standard operating procedure for the beta-testing and clinical trial is discussed in section 4.4.2. The statistical analysis of the metrics was done through the use of artificial intelligence, as discussed in Chapter 5. Classical statistical methods were not complex enough to establish any cause-effect relationships or possible trends (such as linear regression, polynomial regression or logistic regression) between the measured parameters and the presence of ADHD. Machine learning methods were hence used to establish the desired statistically significant relationships between the parameters and the presence of ADHD. Although such relationships could be established, the machine learning tool was not a

standalone diagnostic tool. The reason for this was that a diagnosis for ADHD could only be positive if and only if, six of the nine DSM-V criteria for either of the subtypes (ADHD-hyperactivity or ADHD-inattentive) were present for a period of six months. This was not true for this particular tool for the following reasons: 1) not all the criteria were accounted for, only those that could be quantified and 2) the tool could not directly account for the presence of criteria for a period of 6 months, as required for a positive diagnosis. Furthermore, since most of the criteria for the ADHD-hyperactivity were subjective and could not be translated into measurable parameters, parameters from the ADHD-inattentive criteria were used to model the ADHD-hyperactivity subtype. With the use of artificial intelligence models, this choice of parameter was acceptable since the models would be trained using those parameters, regardless of which subtype of ADHD they were specific to. In conclusion, the tool that was developed was a screening tool. Although it could not provide a clinical diagnosis, it could screen a person using a quantitative approach and determine whether they fell in the ADHD-hyperactivity group or in the normal group.

4.2 Subjects

The subjects consisted of children between the ages of 4 and 17 years old, both male and female (19 male and 11 female). Since the subjects were minor, inclusion was largely based on whether or not parental consent was given to participate in the study. Section 4.2.2 gives a more detailed breakdown of the inclusion and exclusion criteria.

4.2.1 Required Sample Size

According to the sample size estimation in section 4.5, the sample size that yielded the optimal screening accuracy of 90% was 412 samples. However, it was not chosen due to logistical considerations. Using an acceptable screening error of 16% ($\delta = 0.16$) yielded a sample size of 156 samples. Therefore, given a sample size of 156 samples, one could differentiate statistically between a person with ADHD and one without, while having 16% of the results being incorrect, according to the method explained in section 4.5.

4.2.2 Subject Selection: Inclusion and Exclusion Criteria

The main inclusion criteria was age. Since ADHD is most prevalent in minors, the age range was 4 to 17 years old. For children younger than 4 years old and for adults, ADHD becomes less detectable although it may be present (this is especially true for adults). Additionally, only schoolchildren were selected. To avoid bias in the data, gender ratio was kept as closely as possible to 1:1.

In this manner, one could possibly validate the findings in the literature that state that ADHD is more prevalent in boys than in girls.

Demographics were not taken into account when selecting subjects. Rather, the subjects that were chosen came from the private practice of Mrs Rose-Hannah Brown. Nonetheless, when analysing the data, the race of each subject was recorded as an additional feature to use for the statistical model. Feature selection is explained in section 5.

The main exclusion criteria was the presence of photo-sensitive epilepsy in the subjects' medical records. Subjects that suffered from this disorder or had a history thereof were excluded from the study. This precaution was taken because the testing was based on playing a tablet game and this could negatively affect epileptic subjects. Finally, subject participation was voluntary and all subjects could pull out of testing at any point.

4.2.3 Subject Categories

The subjects were classified in the following three categories:

1. ADHD: subjects that have been diagnosed with ADHD in the past six months, without taking into account whether the subjects were under medication or not;
2. Normal (control group): subjects that do not have ADHD or present ADHD-like behaviour.

4.2.4 Ethical Approval

The ethical approval process was administered by the Health Research Ethics Committee (HREC) of Stellenbosch University. According to the HREC, the research was identified as a clinical trial because its purposes were to test effectiveness and efficacy of a diagnosis-aiding tool. The risk of the research was minimal since the testing only consisted of playing a game on a tablet. Ethical approval was obtained on the 14th July 2017 and is valid until the 13th July 2018. It was subsequently extended to July 2019.

4.2.5 Written Consent: Parents

For research involving minors, the HREC requires parental information leaflets that describe the study, as well as parental consent forms. Without these documents, subject participation will not be allowed. The information leaflet gives a clear description of the research to the parents. This includes an overview of what the research entails, a description of the types of tests that will be performed, the responsibilities of the parents, the duration of the tests, the risks involved with the tests and the mitigation thereof, the cost and remuneration

involved (if any), the location of the research site, and how the results will be processed. The contact details of the researchers, participating investigators and HREC are also included in the document.

The consent forms include a declaration for the consenting parent stating that they have read and understood all the information provided by the leaflet. A declaration for the investigator is also included. This declaration states that the investigator has provided all the necessary information pertaining to the research.

4.2.6 Written Assent: Children

For research involving minors, the HREC requires assent from the participants. The form consists of an information leaflet and a declaration. The information leaflet describes to the child what the meaning of research is, what the research is about, why he/she has been invited, the investigators, the research location, the duration of the tests, the details of the tests, the benefits and disadvantages of participating in the research, and contact details of the researchers and participating investigators.

The assent form for the child states that he/she understand what the research is about, that the researcher has answered all of his/her questions, and that he/she can withdraw from the research at any time. Since the age group for minors is large, there are two assent forms provided: one for children between 4 and 11 years old and one for children between 12 and 17 years old. Both forms have the same details and they are presented in an age-appropriate manner.

4.3 Study Design

The study consisted of two main phases: 1) design and development, 2) testing and data collection. The sequence of research activities is illustrated in Figure 4.1 where the testing activities are shown in the lightest blue, the design and development activities are shown in light blue, and the data collection phases are shown in dark blue.

Beta-testing was done in order to collect data and develop a preliminary machine learning model. Cross-validation was done to determine the overall generalization capability of the model. To further validate the results, a randomly selected test set (a subset of the training set) was used to make predictions with the machine learning model. These predictions were then compared to the actual diagnoses given. According to the statistical analysis described in section 4.5, the expected accuracy was 84%, given a sample size of 156. However, the preliminary beta-test model achieved an 85.6% accuracy,

with a sample size of 30.

4.4 Measurement Methods

Every measurement that was taken during the test phase of the study was captured in the back-end of the software game. The advantage of using a software game as a measurement tool was that the sensors and the data acquisition system were all incorporated in the tablet that the game was loaded onto and thus creating a compact, single-device product.

4.4.1 Rationale

The rationale for the measurements was that the DSM-5 diagnostic criteria were translated into measurable parameters and incorporated into the tablet game. This approach ensured that the measurements made by the game were relevant to ADHD on a diagnostic point of view. In summary, the parameters were treated as a quantitative representation of the DSM 5 criteria.

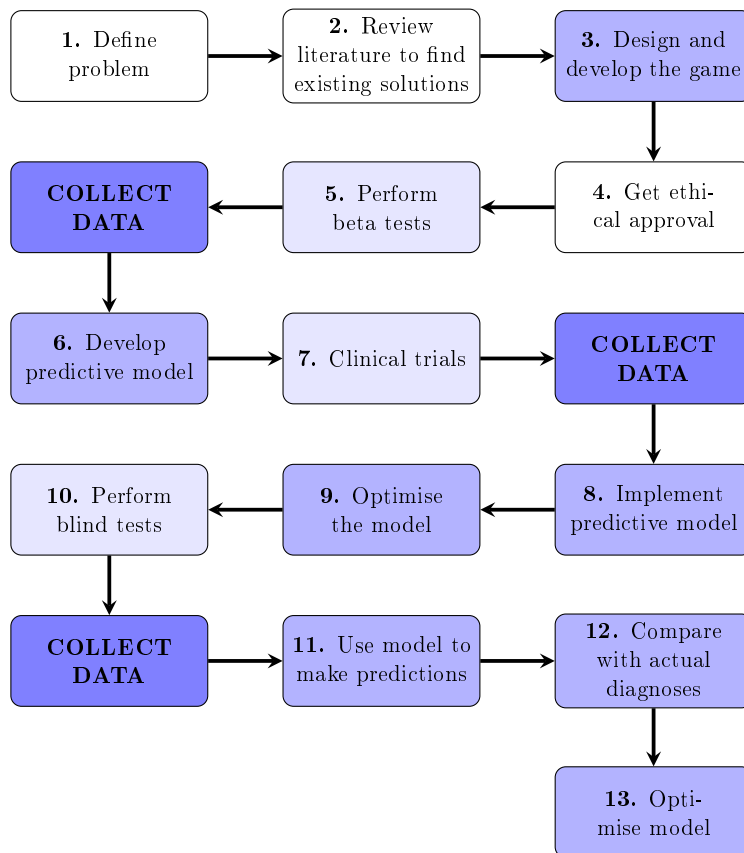


Figure 4.1: Sequence of Research Activities

4.4.2 Standard Operating Procedure

Testing took place at Cape Gate Mediclinic. The role of the investigators during the testing phase included the administration of the game and assisting with any medical needs that could have occurred during game-play.

In the measurement procedure, the test subject was placed in a well-lit room and was seated at a table. The tablet was presented to him/her and placed on the table in front of them. The main investigator explained to the subject what he/she had to do. The game was then launched on the tablet by the investigator and the subject was allowed to play for the maximum duration of the test (8 minutes), unless he/she decided to quit.

For each subject, the investigator recorded their name, age, diagnosis (for control group), race and additional comments/observations into an Excel spreadsheet on the Windows PC. During game-play, the parameters were captured and sent to a FireBase database via a WiFi connection. The data from the database was downloaded by the investigator and loaded into that same Excel spreadsheet for that specific subject. For feedback purposes, the subject was asked what he/she thought of the game, upon completion thereof. Finally, the subject was told to leave the room and the next subject was called in.

One of the key elements of the SOP was that the investigator had to give clear instruction to the subject before launching the game. This was to prevent misuse of the game, although the game mechanic was self-explanatory. The investigator also had to demonstrate to the subject how to hold the device to ensure that he/she feels comfortable when playing the game since for some tasks, the device had to be held in order to capture meaningful data from the accelerometer and gyroscope sensors.

4.4.3 List of Parameters

The parameters that were monitored are shown in Table 3.1. The applicable DSM-5 criteria, units and description of each parameter are also given. It must be noted that the listed parameters do not represent all of the measurements but rather the main types of measurements.

4.5 Analysis

Meaningful results could only be attained through well-planned statistical analysis. The first step of the analysis was to consult with one of the University's statisticians, Prof. D.G Nel. His recommendation was used to determine an estimate for the sample size as discussed in a subsequent section.

4.5.1 What was Analysed between Subgroups?

Data analysis was done using machine learning methods, as discussed in chapter 5. The advantage of machine learning is its ability to train itself given enough samples and pick up on trends that the traditional statistical methods could overlook. Nonetheless, when comparing the different subgroups, the parameters that were expected to be significantly different were analysed. This included task completion time, number of mistakes and device motion.

Through simple statistical analysis such as linear regression, it was seen that there were meaningful differences in these parameters for the different groups. Preliminary analysis between subgroups was necessary in giving an indication of whether or not more complex analyses such as machine learning would work. However, the failure of preliminary analysis to reveal any meaningful trends did not imply that machine learning would fail too.

4.5.2 Sample Size Estimation

The method used to determine sample size was the POWER analysis. This method was applied to the McNemar test. In the McNemar test a 2 x 2 contingency table as seen in Table 4.1 is used to compare two different test methods that have the same outcome. The parameters a , b , c and d are the number of samples for each category and N represents the total number of samples.

Table 4.1: McNemar Test: 2 x 2 Contingency Table

	Method 1 Positive	Method 1 Negative	Row Total
Method 2 Positive	a	b	$a + b$
Method 2 Negative	c	d	$c + d$
Column Total	$a + c$	$b + d$	N

In this research, Method 1 is analogous to the current diagnostic methods (as explained in section 2.2). Method 2 is analogous to the new method produced by the research. For both methods, positive refers to the presence of ADHD in a sample while negative refers to the absence thereof.

For the McNemar test, the null hypothesis of marginal homogeneity states that the two marginal probabilities for each method are the same [45]. This can be written mathematically as

$$H_0 : \delta = 0 \quad (4.1)$$

$$H_1 : \delta \neq 0 \quad (4.2)$$

δ represents the difference in the population proportion when a positive outcome occurred in Method 1, and the population proportion when that same outcome occurred in Method 2. In other words, the difference in population proportion when Method 1 was positive and the population proportion when Method 2 was positive (the same can be calculated for when both methods were negative). Mathematically δ can be expressed as

$$\begin{aligned}\delta &= \frac{a+c}{N} - \frac{a+b}{N} \\ \delta &= \frac{c-b}{N}\end{aligned}\tag{4.3}$$

To determine an estimate for the sample size, a POWER analysis was done using Statistica. The expertise of qualified statistician, Prof. D.G. Nel was solicited. The input parameters that were required by Statistica were the following:

- (i) δ : the difference in population proportion when Method 1 was positive and the population proportion when Method 2 was positive as described in McNemar's method;
- (ii) η : the total proportion of times different events occur for the two methods (also referred to as the nuisance parameter). This was chosen as 0.4 based on the statistician's recommendation;
- (iii) α : the type 1 error-rate. This value is taken as 0.05 and means that one is willing to accept that there is a 5% chance that the null hypothesis is wrong. 0.05 is the standard accepted value for α (try to find reference);
- (iv) Power goal: in Statistica, the power goal refers to the minimum power to be achieved when searching for an acceptable sample size. This value was chosen as 0.9 based on the statistician's recommendation.

The POWER analysis was applied to various cases where the value of δ was changed as shown in Table 4.2. To stay as close as possible to the null hypothesis in equation (4.1), δ was kept less than 20%. Figures 4.2 to 4.7 give graphical representations of the POWER calculations for the cases in Table 4.2.

The significance of the value of δ is the error in distinguishing between the two methods. In this case, Method 1 is analogous to the current diagnostic methods (gold standard) and Method 2 is analogous to the new developed method. For each POWER analysis case, a power graph was obtained. The general trend of the power graph was that it resembled an exponential function, where the required sample size (N) increased rapidly with small increases in the power goal. Given the parameters in Table 4.2, the power graphs show that changing δ values resulted in different ranges for possible N values. For

Table 4.2: POWER Analysis

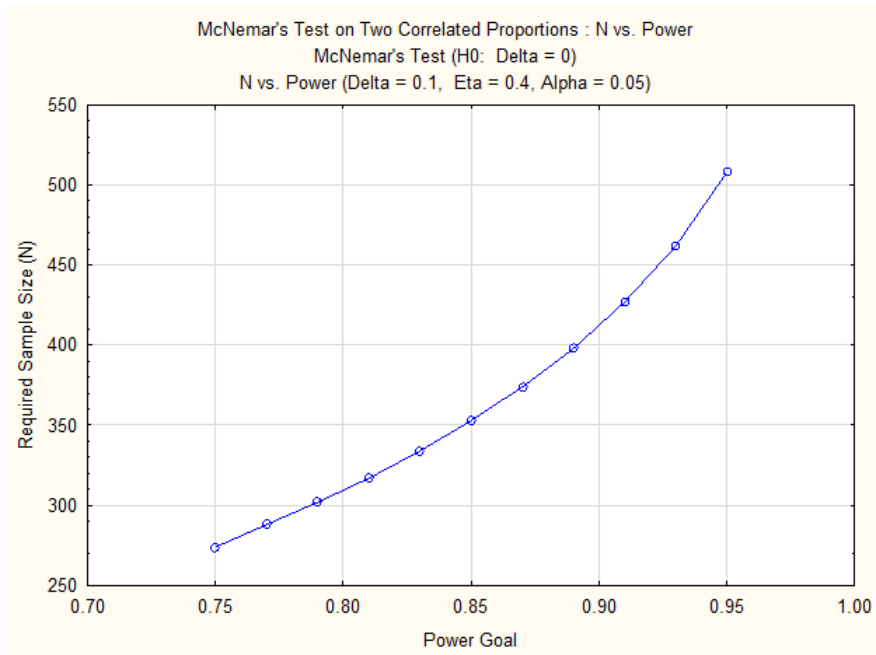
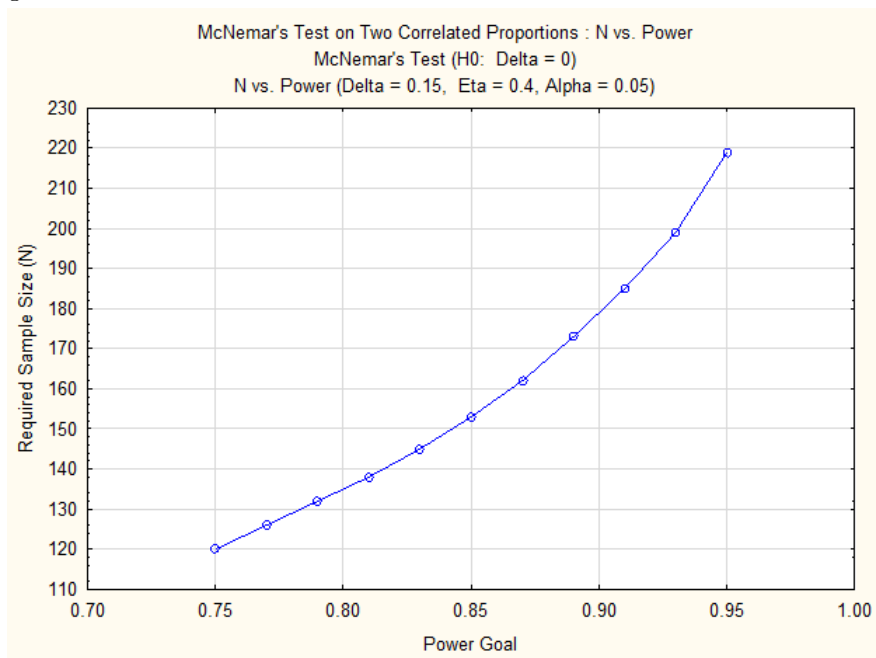
δ	η	α	Power goal	Actual Power for Required N	Required Sample Size
0.1	0.4	0.05	0.9	0.9004	412
0.15	0.4	0.05	0.9	0.9003	178
0.16	0.4	0.05	0.9	0.9016	156
0.17	0.4	0.05	0.9	0.9013	137
0.18	0.4	0.05	0.9	0.9009	121
0.2	0.4	0.05	0.9	0.9002	96

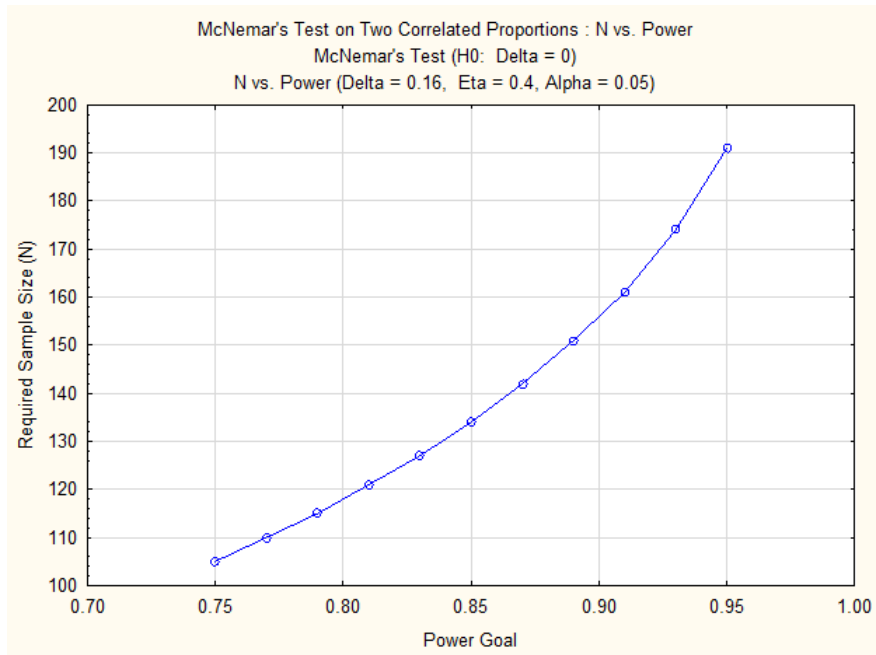
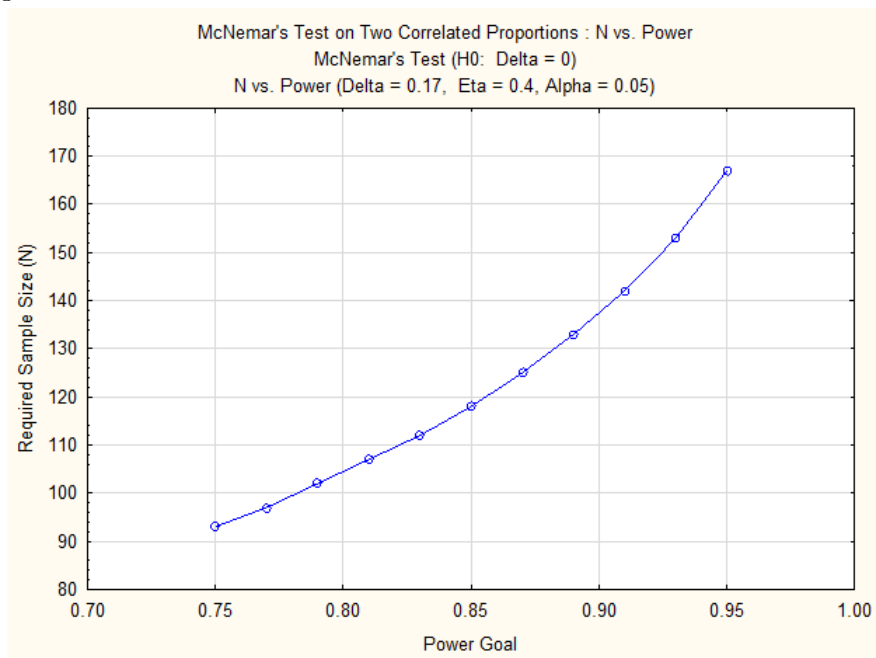
small values of δ ($\delta = 0.1$) the required sample size given a power goal of 0.9 was large. For the larger values of δ ($\delta = 0.2$), N was smaller than 100.

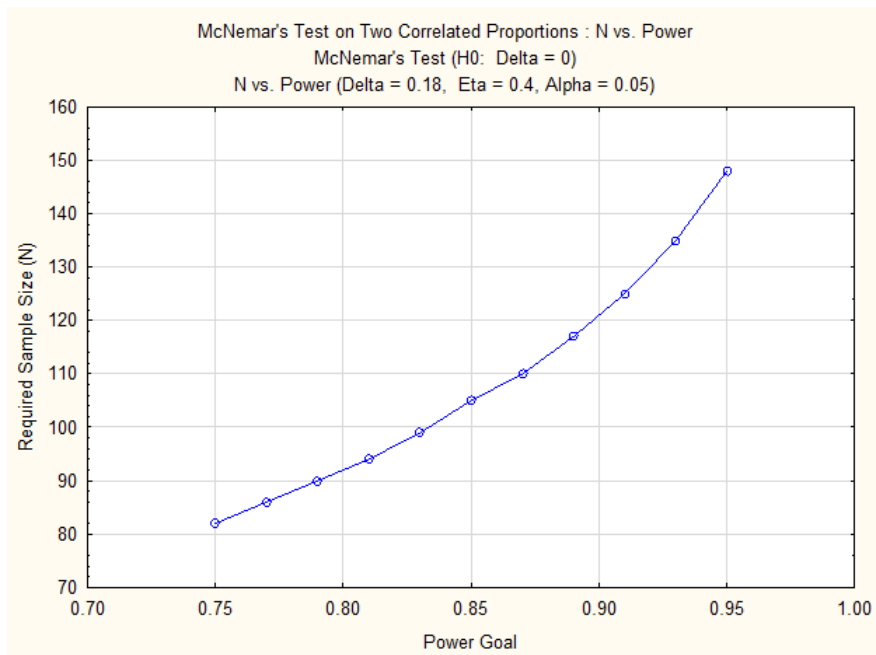
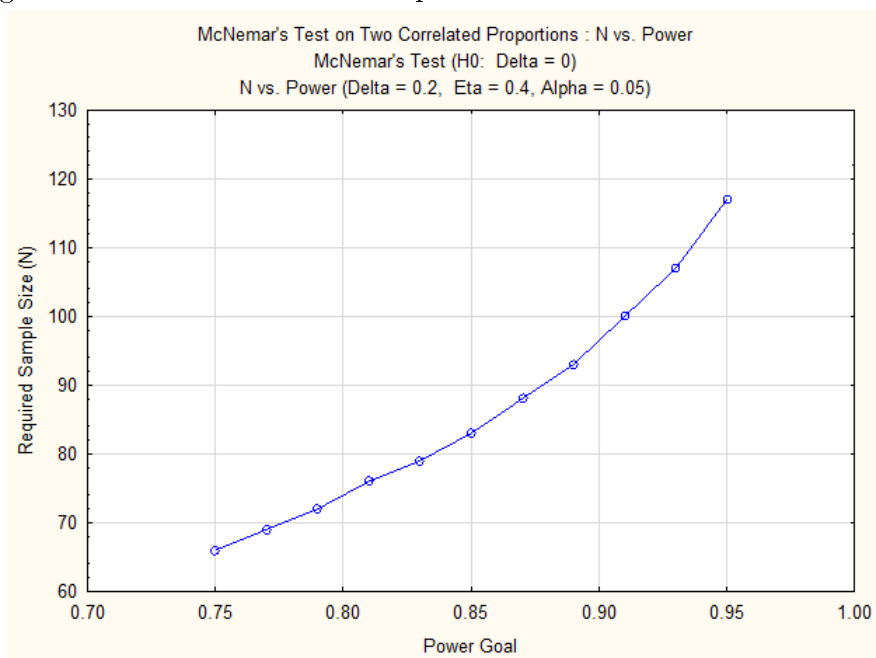
The required sample size that was chosen was 156 subjects. This occurred with $\delta = 0.16$. In other words, the error in distinguishing between the gold standard method and the new method was 16% (84% accuracy). However, the final recommendation on the sample size was 200 subjects. The additional 44 subjects were used as test subjects for the machine learning algorithms while the other 156 subjects were used to train the machine learning algorithms.

4.5.3 Structure of Study Database

Once an estimate for sample size and the list of measurements were determined, a database structure was implemented. The key aspect of the database was that it was created using FireBase, a cloud-based system and could therefore be downloaded (in .txt or .csv formats) solely by the investigators, to increase data security. For each subject that was tested, a new FireBase entry was created and the time and date of the entry was. When creating the statistical model, all of the FireBase entries were downloaded into a single matrix where each row represented one subject and each column represented a feature.

Figure 4.2: McNemar Test: Sample Size Determination with $\delta = 0.1$ Figure 4.3: McNemar Test: Sample Size Determination with $\delta = 0.15$

Figure 4.4: McNemar Test: Sample Size Determination with $\delta = 0.16$ Figure 4.5: McNemar Test: Sample Size Determination with $\delta = 0.17$

Figure 4.6: McNemar Test: Sample Size Determination with $\delta = 0.18$ Figure 4.7: McNemar Test: Sample Size Determination with $\delta = 0.2$

Chapter 5

Machine Learning

Machine learning has gained traction in data processing applications. The significance of the use of machine learning is that it can identify trends and correlations that could not be picked up by traditional statistical methods. The ability of machine learning algorithms to train themselves given a training dataset is also an advantage because models can be accurately developed using specific datasets. There are various kinds of machine learning algorithms, each suited for specific applications. For this study, the approach that was taken for developing the machine learning model was to implement a support vector machine classifier (SVM) with a linear kernel. Two datasets were used to extract one feature set that contained gameplay feature, as well as statistical features from the accelerometer sensor. All the machine learning implementation was done in MATLAB. This chapter begins with a brief description of the datasets that were used. Next, feature extraction is explained and this is followed by feature selection. Two feature selection methods are analysed. Finally, the chapter ends with a description of the classifier using the best feature set.

5.1 Datasets

Two datasets were obtained during the beta-tests. The first one was the gameplay dataset, which consisted of game-play variables as described in 3.3. The second dataset was the accelerometer raw data from the x, y and z axes. Features were extracted from both of these datasets to form a single feature matrix that was used to develop the classifier.

5.1.1 Distribution of Data

A total of 30 subjects took part in the beta-test. Subject age ranged between 6 and 17 years of age. Table 5.1 gives a breakdown of the subject distribution. Due to ethical considerations, all subjects were kept anonymous and only assigned a unique identifying number.

Table 5.1: Breakdown of Subject Distribution

Category	Value
Mean subject age	10 years old
Maximum subject age	16 years old
Minimum subject age	5 years old
Male subjects	15
Female subjects	15
ADHD male subjects	6
ADHD female subjects	7
Non-ADHD male subjects	10
Non-ADHD female subjects	7
Total subjects	30

5.1.2 Train-test Set Split

In order to train the classifier, the aggregate feature matrix was split into a training set, and test set. The split between the two sets was that approximately 75% of the dataset was used for training, while the other 25% was used for testing. Since the dataset was small, leave one out cross-validation was used (LOOCV). This type of cross-validation is explained in section 5.4. The test set was kept separate and used as new and “unseen” data into the trained classifier. Table 5.2 shows how the data was split into the three different sets. The split was done by choosing random observations and allocating them to each of the sets according to the split ratio.

Table 5.2: Training and Test Set

Set	% full set	number of samples
Training	75	23
Test	25	7

5.2 Feature Extraction

Feature extraction is an important step in building a classifier, as it allows for raw data to be interpreted into meaningful information that can help the classifier distinguish one observation from another.

5.2.1 Outlier Detection and Treatment

Prior to calculating features to extract, outlier detection was performed. The method used took the interquartile range (IQR) into account where

$$IQR = Q_3 - Q_1 \quad (5.1)$$

Q_3 and Q_1 represent the middle values of the first and third half of the dataset respectively. A data-point x_i was seen as an outlier if it satisfied one of the following two conditions:

$$\begin{aligned} x_i &> Q_3 + 1.5IQR \\ x_i &< Q_1 - 1.5IQR \end{aligned}$$

If either of the conditions were met, then x_i was replaced by the equation proposed by [46]:

$$x_i = \frac{x_{i-1} + x_{i+1}}{2} \quad (5.2)$$

This equation was also applied for the accelerometer dataset in order to clean it out. A visual representation of outlier detection is to use box-and-whisker plots. This is shown in Figure 5.1 for the game-play feature matrix F_g . It is seen that only the throws feature had an outlier, which was replaced using equation 5.2.

5.2.2 Game-play Dataset

For the game-play dataset, a feature matrix labelled F_g was used to store the extracted features. The matrix F_g was in the form

$$F_g = [f_1 \ f_2 \ f_3 \ f_4 \ \dots \ f_k]$$

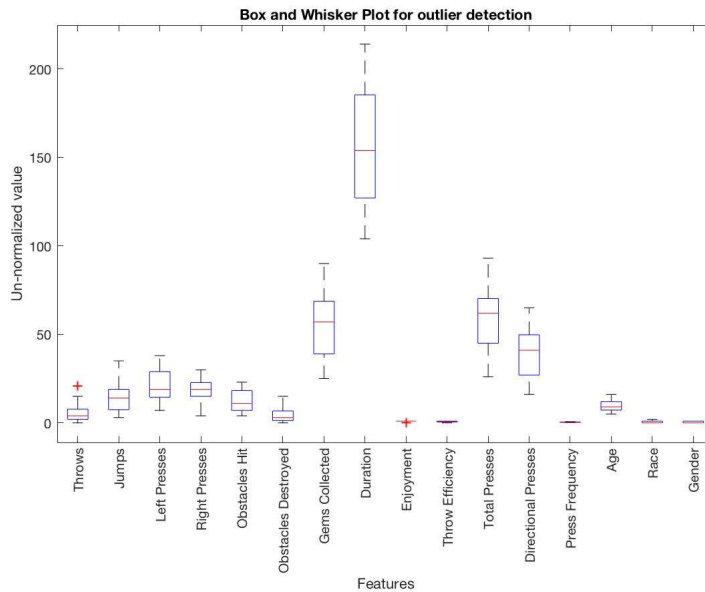


Figure 5.1: Box-and-whisker Plot of F_g

where k was the number of features. In addition to the features listed in 3.3, four more features were created: throw efficiency, total button presses, directional button presses and frequency of button presses. The throw efficiency (TE) feature was calculated as follows:

$$TE = \frac{\text{obstacles destroyed}}{\text{total button presses}} \quad (5.3)$$

The frequency of button presses (FBP) feature was calculated as follows:

$$FBP = \frac{\text{total button presses}}{\text{game duration}} \quad (5.4)$$

Additionally to these features, user features were also added to F_g . The full list of features in F_g was as follows: number of left button presses, number of right button presses, number of jumps, number of throws, number of obstacles destroyed, number of obstacles hit, number of gems collected, game duration, game enjoyment (boolean: 1 = enjoyed, 2 = did not enjoy), throw efficiency, total button presses, directional button presses, frequency of button presses, age, race and gender. This resulted in $k = 16$.

Feature normalization was performed on F_g in order to ensure efficient classifier training. The intuition with feature normalization is that each feature is mathematically transformed to have zero mean. Therefore, for each feature f_i in F_g (where $i = 1, 2, \dots, k$), the following applies

$$f_i = \frac{f_i - \mu_i}{s_i} \quad (5.5)$$

where μ_i is the average of all the observations for that feature and s_i is the range of the observations of that feature.

5.2.3 Accelerometer Dataset

The accelerometer dataset contained raw time-series data from the x, y and z axes. Two types of features were extracted from these time-series: 1. statistical features and 2. morphological features. These types of features have been demonstrated to provide good classifier performance [46]. Furthermore, the modulus of the acceleration was also used as an additional time series to extract features from. The modulus was calculated as

$$a_{total} = \sqrt{a_x^2 + a_y^2 + a_z^2} \quad (5.6)$$

For the accelerometer dataset, a feature matrix labelled F_a was used to store the extracted features. The matrix F_a was in the form

$$F_a = [f_1 \quad f_2 \quad f_3 \quad f_4 \quad \dots \quad f_n]$$

where n was the number of features.

Statistical Features

Statistical features were calculated on the dataset using some of MATLAB's built-in functions. Out of all the features, only the crest factor did not make use of MATLAB's library functions. The crest factor was calculated as follows:

$$CF = \frac{f_{min} - f_{max}}{f_{rms}} \times 0.5 \quad (5.7)$$

where the numerator is the range and the denominator is the root mean square (RMS). The following 18 statistical features were extracted: mean, standard deviation, minimum, maximum, range, median, sum, variance, skewness, kurtosis, RMS, percentiles (10th, 25th, 50th, 75th and 90th), interquartile range (IRQ) and crest factor. This resulted in a total of 72 features (18×4), where each of these features was calculated for the x, y, z axes and for the modulus.

Morphological Features

Morphological features were those features that could be extracted by the visual characteristics of the raw signals. The exact euclidean distance was used to determine the distance between each of the three axes. It was therefore calculated for the x-y, x-z and y-z pairs using the following equation:

$$ED = \sqrt{\sum_{i=1}^m (q_i - c_i)^2} \quad (5.8)$$

where the two time series $Q = q_1 \dots q_m$ and $C = c_1 \dots c_m$ are evaluated. The next feature that was calculated was autocorrelation coefficient r_1 . The autocorrelation coefficient indicates how successive values of a given signal relate to each other. The following equation was used for r_1

$$r_1 = \frac{\sum_{t=2}^m (Y_t - \bar{Y})(Y_{t-1} - \bar{Y})}{\sum_{t=1}^m (Y_t - \bar{Y})^2} \quad (5.9)$$

where \bar{Y} is the mean of signal Y . Zero-crossing detection was used to count the number of x-intercepts of a signal. This was done using a built-in MATLAB function "dsp.ZeroCrossingDetector". Area features were also calculated for the signals. This included positive area, negative area, total area, absolute total area and total absolute area. The distinction between the absolute total area and the total absolute area was that the former was calculated as follows:

$$ATA = |Total Area| \quad (5.10)$$

while the total absolute area was calculated as:

$$TAA = Area_{positive} + |Area_{negative}| \quad (5.11)$$

Additionally, a feature was calculated for latency time. Latency time was the time at which the maximum value of a signal occurred. To summarize, the following 10 morphological features were extracted: exact euclidean distance, autocorrelation coefficient, positive area, negative area, total area, absolute total area, total absolute area, number of zero crossings, latency time, peak-to-peak time-window. This resulted in a total of 39 features ($10 \times 4 - 1$), where each of these features was calculated for the x, y, z axes and for the modulus, except for the exact euclidean distance which was only calculated for the three possible axis pairings.

Normalization

The final step in forming the feature matrix F_a was to normalize its elements so as to achieve high efficiency when creating the classifier. Equation 5.5 was also used here for normalization.

5.3 Feature Selection

The feature matrices F_g and F_a were appended to form one feature matrix F for the classifier. Prior to this step, a preliminary feature selection test was done, as described in the subsequent section. Three primary feature selection methods were used. The feature subset that yielded the best classification results was used. The three methods were: 1. brute/manual feature selection, 2. principal component analysis and 3. genetic algorithm. These methods are described after the preliminary feature selection section.

5.3.1 Preliminary Feature Selection

The test consisted of generating a correlation matrix using MATLAB's "corr" function for F_g and determining whether or not there were any strong linear correlations between any pairs of features (indicated by coefficient value between 0.95 and 1). If this was true, then one of the features from the pairs was removed, depending on the qualitative information that that feature gave. Figure 5.2 shows the correlation matrix of F_g .

As expected, the correlation coefficients along the diagonal are 1, since it represents correlation of a feature with itself. It can be seen that there are two strong correlation pairs. The first one between the number of obstacles destroyed and the number of throws. This is strong correlation is expected since the number of obstacles destroyed directly relates to the number of throws.

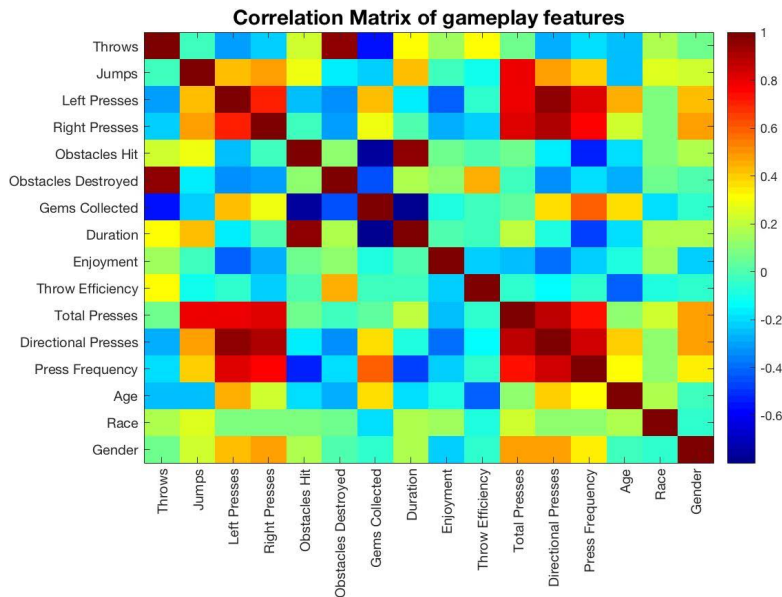


Figure 5.2: Correlation Matrix of Game-play Feature Set

The second pair is between the duration of the game and the number of obstacles hit. This correlation is unexpected since it is difficult to relate these two features without the use of this matrix. As a result, only the first pair was considered and the obstacles destroyed feature was removed.

Similarly, a correlation matrix was generated on the feature matrix F (aggregate features). This is shown in Figure x. It can be seen that there were no strong correlation pairs, therefore no features could be removed. Ultimately, this method of visually inspecting the correlation matrices allowed for one redundant feature to be removed.

Table 5.3 shows the breakdown of the feature set. A total of 127 features were extracted, the majority of them being statistical features. The use of statistical features on time-series is well demonstrated in [47]. Morphological features were the second group of features. It is seen in [48] that morphological features can be useful to characterize a time-series. The user features included those that were directly related to the demographic of the subjects. Finally, the game-play features were the ones that were directly extracted during game-play. An additional set of features was calculated based on the game-play parameters.

5.3.2 Primary Feature Selection

Various methods are proposed for feature selection. The most straight-forward method is called brute-force selection approach, also known as exhaustive search. This method uses all possible combinations of features. So, given

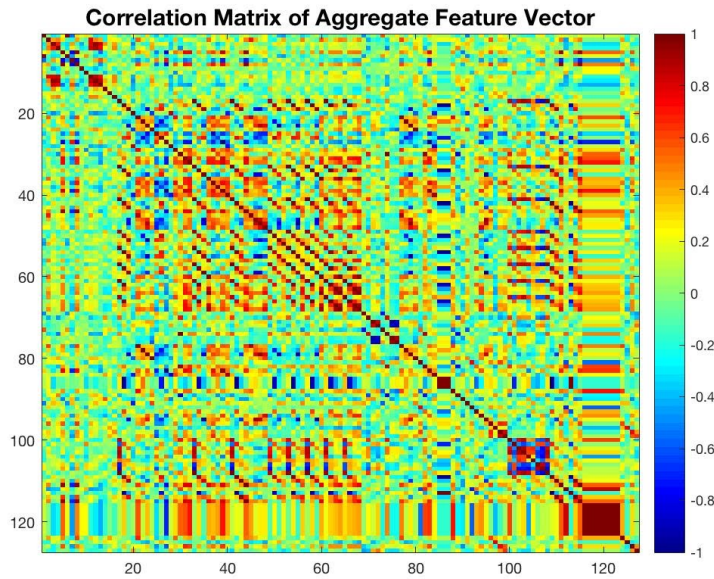


Figure 5.3: Correlation Matrix of Aggregate Feature Set

Table 5.3: Breakdown of Feature Set

Feature type	Number of features
Statistical	72
Morphological	39
Game-play features	8
Game-play-derived features	4
User features	3
Total features	126

k features, $2^k - 1$ combinations are possible. This resulted in $2^{126} - 1 = 8.5e^{37}$ combinations for the features extracted in the study. Practically speaking, using brute force is not feasible in finite time.

Other methods and algorithms were thus used. In the study, five feature subsets were selected using sequential forward selection (SFS) and manual selection. The six resulting subsets are shown in Table 5.4. It can be seen that applying feature selection helped reduce the dimensionality of the original feature set and thus improve efficiency of the classifier performance. The method that reduced the dimensionality the most was the SFS method used on the full feature set. The SFS method was applied on the whole feature set to produce the subset F_{SFS} , while $F_{combined}$ was a result of applying SFS to the game-play dataset F_g and adding this to F_{SFS} . The manual methods involved applying SFS to the game-play feature set F_g and combining it with manually selected features from the accelerometer feature set F_a . The best

Table 5.4: Feature Subsets

Feature subset	Selection method	Number of features
F_{all}	All features used	126
F_{SFS}	SFS	10
$F_{combined}$	SFS	21
F_{man1}	SFS and manual	83
F_{man2}	SFS and manual	55

feature subset was chosen based on its minimum LOOCV accuracy.

Leave-One-Out Cross-Validation

The LOOCV method can be used for small datasets, as it gives a more robust generalization error, as opposed to using a full validation set. LOOCV works as follows:

1. Given a training set with n observations, split the training set into a training subset and a test subset;
2. Set the test subset to be one single observation from the training set;
3. Set the training subset to be all the other observations from the training set, that is, training subset should have $n - 1$ observations;
4. Use the training subset to train the classifier;
5. Use the classifier to predict the output of the test subset;
6. Use a mean squared error (MSE) function (or some other error function) to determine the error between the prediction and the actual target value of the test subset observation. MSE is given by

$$MSE = (y_{out} - y_{pred})^2 \quad (5.12)$$

where y_{out} is the target value of the observation that was left out and y_{pred} is the predicted output;

7. Repeat step 2 while choosing a different observation;
8. Repeat steps 3 - 6;
9. Repeat steps 7 - 8 until each observation has been singled out, that is n times;
10. Take the sum of each iteration's MSE and divide it by n to get the LOOCV error

$$CV_n = \frac{1}{n} \sum_{t=1}^n MSE_i \quad (5.13)$$

Case 1: All Features Selected

The initial approach was to use all the features. Since the number of features was relatively small, this was seen as a feasible option. The disadvantage to this approach was that there was no feature ranking or feature importance, as all the features were present.

Case 2: Sequential Forward Selection

With the SFS method, features are sequentially added to the feature set, using some criterion. SFS is one of the simplest sequential selection algorithms. It is as follows:

1. Start with an empty feature set $F_0 = 0$;
2. Select the next best feature f such that the objective function $J(F_k + f)$ is maximized when combined with the features that have already been selected;
3. Update Y_{k+1} ;
4. Repeat 2 and 3.

SFS was implemented in MATLAB using the “sequentialfs” function which takes on as inputs the following parameters: a function handle to the objective function, a dataset with observations or samples and the direction of selection (forward in this case). The objective function that was used was a linear regression model. The output of the function is a logical row vector of length k , where k is the number of variables in the input dataset. The logical row vector contains 1’s at the indexes of the selected variables. The full feature set was used with this implementation. This resulted in the 10 following features: number of obstacles hit, crest factor of modulus, total absolute area x-axis, positive area x-axis, positive area z-axis, latency time z-axis, peak-to-peak time window of modulus, 25th percentile z-axis and skewness z-axis.

Case 3: Sequential Forward Selection on Combined Sets

SFS was applied to the game-play feature set to form a new subset of features. This new subset was then combined to the subset described in the previous case. The SFS method was able to select the following 11 game-play features: number of left presses, number of right presses, obstacles hit, gems collected, game duration, game enjoyment, throw efficiency, button press frequency, age, race and gender. The new feature subset therefore included 21 features.

Case 4: SFS and Manual Selection

The fourth approach was to once again use the selected game-play features from the SFS method and combine those with: 1. accelerometer morphological

features 2. accelerometer statistical features. Thus resulting in two additional subset of features containing 83 and 25 features respectively.

5.4 SVM Model Selection

The approach that was taken in building the SVM classifier was based on the recommendation given in [49]. The method was as follows:

1. Transform data into the format for the SVM package;
2. Perform simple scaling and normalization on the data;
3. Consider the linear kernel ([38] agrees with this)
4. Tune the parameter C by using cross-validation (in the case of this study, LOOCV was used instead);
5. Use the tuned parameter C to train the whole training set
6. Test

In the study, the classifier performed binary classification where the target outputs were given by either 1 (presence of ADHD) or 0 (non-ADHD). As explained, the model was developed in MATLAB, using the built-in “fitcsvm” function. The inputs of the function were the following:

1. A scaled and normalized dataset X ;
2. Target values y , where $y \in [01]$;
3. Regularization parameter C . This parameter adds a penalty to features, thus reducing their overall effect. It is tuned to limit over-fitting;
4. The kernel type (linear);

The output of the function was a model in the SVM package format. As explained in section 5.2, LOOCV was used for validation. Furthermore, five classifiers were developed for the LOOCV algorithm, each one corresponding to a feature set as derived in 5.4. The procedure that was used was the following:

1. Choose an initial value for C : $C = 10$;
2. Perform LOOCV on each of the five feature sets F_{all} , F_{SFS} , $F_{combined}$, F_{man1} , F_{man2} . Five models were developed for LOOCV:
 - i MODEL1 = fitcsvm(F_{all}, \dots);
 - ii MODEL2 = fitcsvm(F_{SFS}, \dots);
 - iii MODEL3 = fitcsvm($F_{combined}, \dots$);

- iv MODEL4 = fitcsvm(F_{man1}, \dots);
 - v MODEL5 = fitcsvm(F_{man2}, \dots);
3. Report LOOCV error of each classifier;
 4. Repeat steps 1 to 3 for a few different values of C : $C = 3, 1, 0.3$;
 5. Choose feature set with the lowest LOOCV error;
 6. Use the corresponding C value to build a final model;
 7. Train the model using the whole training set (not just a subset of the training set unlike in LOOCV);
 8. Use the test set to predict outputs;

Table 5.5 shows the results of LOOCV error calculated for different C values and for the different feature sets. This approach resulted in a tuned parameter C , as well as an optimal feature set. It is clear from the table that the feature set with the highest error was the one that included all features. This was expected due to the higher dimensionality. The feature with the least features appeared to have been the optimal one, consistently showing low error on all values of C . Furthermore, there is some relationship between the number of features and the error: the higher the number of features, the higher the error. Ultimately, after using the smallest C value, it was seen that the combined feature set $F_{combined}$ outperformed the F_{SFS} set in terms of error. Therefore feature set that was thus chosen was $F_{combined}$, where the minimum error of 16.5% was found. Furthermore, the optimal C value was $C = 0.3$. Intuitively, $F_{combined}$ is a better representation of the feature set than F_{SFS} since the former contains more representative features of the whole feature set.

The last step in developing the SVM model was to train the classifier using the tuned parameter $C = 0.3$ and the feature set $F_{combined}$. Previously, the classifier was trained for LOOCV using only a subset of the training set of $F_{combined}$. Now, the classifier is trained using the whole training set. This resulted in the following model

$$MODEL = fitcsvm(F_{train}, C, \dots)$$

Table 5.5: LOOCV Error on Different Feature Sets and Various C values

Feature set	# features	$C = 10$	$C = 3$	$C = 1$	$C = 0.3$
F_{all}	126	0.5	0.5	0.5	0.5
F_{SFS}	10	0.25	0.1875	0.1875	0.1875
$F_{combined}$	21	0.4375	0.4375	0.415	0.165
F_{man1}	83	0.46	0.4375	0.437	0.437
F_{man2}	55	0.43	0.4	0.4	0.4

The model was then used on the test set to make predictions using MATLAB's built-in “predict” function, which took MODEL and the test set as inputs and returned a row vector of predicted outputs. The results and performance of the classifier are discussed in the next chapter.

Chapter 6

Results and Discussion

6.1 Results

As mentioned previously, the small sample size that was used for the study induced certain limitations. Chief among them is the validity of the results. However, the results that will be discussed in this section are suggestive rather than conclusive.

The main results of the performance of the classifier can be seen in the confusion matrix in Figure 6.1. These results came from the test set. Since training accuracy is not a good indication of a classifier's performance, the training set confusion matrix was not calculated. Various performance metrics were derived from the confusion matrix and are explained next.

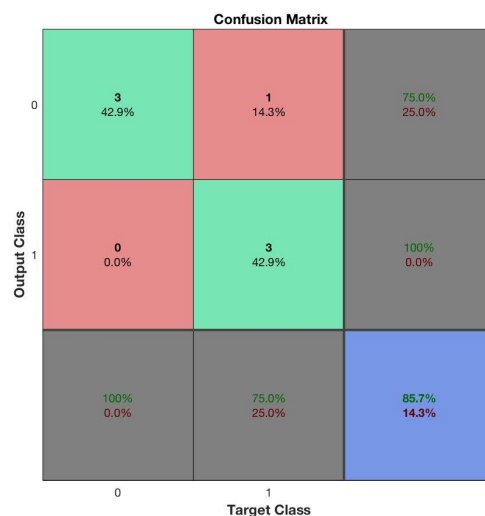


Figure 6.1: Confusion Matrix of SVM Classifier

According to the confusion matrix, there were three true positives (TP), three true negatives (TN), one false negative (FN) and no false positives (FP). The following equations show the metrics that were used to evaluate performance. The accuracy or test set accuracy was calculated in the following way:

$$ACC = \frac{TP + TN}{TP + TN + FP + FN} \quad (6.1)$$

The true positive rate (TPR), also known as the sensitivity or recall, was given by

$$TPR = \frac{TP}{TP + FN} \quad (6.2)$$

The true negative rate (TNR), also known as the specificity, was given by

$$TNR = \frac{TN}{TN + FP} \quad (6.3)$$

The positive predictive value (PPV), also known as the precision, was given by

$$PPV = \frac{TP}{TP + FP} \quad (6.4)$$

The negative predictive value (NPV) was given by

$$NPV = \frac{TN}{TN + FN} \quad (6.5)$$

The F_1 score which represents the harmonic mean of precision and sensitivity, was given by

$$F_1 = 2 \frac{PPV \times TPR}{PPV + TPR} \quad (6.6)$$

The false positive rate α , also known as the type I error, was given by

$$\alpha = 1 - TNR \quad (6.7)$$

The false negative rate β , also known as the type II error, was given by

$$\beta = 1 - TPR \quad (6.8)$$

The values of the performance metrics are shown in Table 6.1. It can be seen that the test set accuracy and LOOCV accuracy are both high. This is expected given a small dataset. The sensitivity (TPR) relates to the classifier's ability to classify ADHD test subjects as having ADHD. Sensitivity is therefore an important characteristic of the classifier, especially if screening is involved. Good classifier performance would require for the classifier to correctly identify subjects that are ADHD. Here the sensitivity is 0.75. This

Table 6.1: Performance Metrics of SVM classifier on Test Set

Metric	Symbol	Value
LOOCV Accuracy	CV	0.835
Test Accuracy	ACC	0.857
True positive rate	TPR	0.75
True negative rate	TNR	1.00
Positive predictive value	PPV	1.00
Negative predictive value	NPV	0.75
Harmonic mean	F_1	0.857
Type I error	α	0.00
Type II error	β	0.25

means that 75% of the time, the classifier will be able to detect the presence of ADHD. Although ADHD is sometimes difficult to detect, even with classical methods, a sensitivity of 75% is quite low. The specificity (TNR) relates to the classifier's ability to correctly reject non-ADHD test subjects. Therefore, the specificity is the proportion on non-ADHD test subjects that will be classified by the classifier as not having ADHD. Since the specificity here is 1, it shows that all non-ADHD test subjects were correctly classified.

The PPV relates to the relevance of the outputs that were classified. A precision of 1 means that all the outputs that were classified were relevant. The NPV shows that 75% of relevant targets were selected.

The F_1 score, mathematically speaking, is the harmonic mean of the precision and recall. In other words, it shows the balance between precision and recall. Values of F_1 that are very high or very low, show that precision and recall are not well balanced. This appeared to be the case with this classifier. The high value of 85.7% suggests that the model may have high precision and low recall, or vice versa.

The type I error of 0 suggests that the null hypothesis was true, and accepted. Although this metric is not indicative given the dataset, it would have been approximately equal to 0.05 for a larger set. The type II error of 0.25 is quite large and suggests that there is 25% probability that the classifier may predict false positives.

In addition to the performance metrics that were discussed, a comparison of the test set distribution and target set distribution was made. The following observations were made:

- The target values comprised of 4 ADHD subjects and 3 non-ADHD subjects;

- The predicted values comprised of 3 ADHD subjects and 4 non-ADHD subjects;
- The test set comprised of 2 boys, 1 of which was ADHD;
- The test set comprised of 5 girls, 3 of which were ADHD;
- All the boys with ADHD were classified correctly;
- All the boys without ADHD were classified correctly;
- Out of the 3 girls with ADHD in the test set, 2 were classified correctly;
- All the girls without ADHD were classified correctly.

Although no major conclusions can be drawn from these few observations it is interesting to note that the classifier was able to correctly reject all the boys and girls that didn't have ADHD, as suggested by the 100% specificity. Contrary to the claim that boys are more misdiagnosed than girls, the test set shows that all boys were correctly classified. This observation does not resolve the claim, however, since the dataset was not representative enough of a wider ADHD population. It is also seen from these observations that the recall of 75% is evident: 3 out of 4 ADHD subjects were predicted.

6.2 Discussion

As a concluding remark to the interpretation of the results, what was seen was that a classifier's performance does not solely rely on its test and cross-validation accuracies. Although cross-validation is a robust way to build classifiers and gives a general indication of how well the model will perform, models should be chosen based on their practical application as well. For example, the classifier built for this study was to be used for screening of ADHD. This means that other metrics become very relevant for assessing the model. Such metrics include sensitivity, specificity and recall.

According to the statistical analysis that was done to estimate a sample size (chapter 4), it was recommended that a total of 200 subjects be used in order to achieve a model accuracy of 84%. The main aim of the study was to conduct a clinical trial, given this sample size. The first step was to perform beta-tests on a smaller population ($N = 30$) in order to demonstrate the validity of the use of machine learning models. Although the beta-test results were seen as preliminary results, they were indicative enough to be used to demonstrate that the research question could be answered. Given the time constraints on the study, it was decided that clinical trials would form part of future work. The aim was to develop a screening tool for ADHD, and the beta-test was able to provide a solution for that. Nonetheless, this does not

imply that the model that was developed is not subject to further optimizations. Such optimizations will be discussed in the next chapter.

Chapter 7

Conclusion and Recommendations

7.1 Conclusion

The overall objective of the study was to develop a screening tool for ADHD using quantitative methods. In order to achieve this outcome, the overall objective was broken down into measurable objectives, as discussed in the introduction. All of these objectives were successfully achieved, except for the clinical trial phase that was not conducted. Prior to this phase, a beta-testing phase was done and it was seen that the results from this phase were acceptable. Furthermore, due to logistical considerations, the planned clinical trial could not be done and completed in time. Therefore, the results of the beta-testing phase, which could be seen as preliminary, were used instead.

The study began by analyzing some current methods that are used in the field, as well as their shortcomings. This literature served as proof in determining the need for a novel method to provide screening for ADHD. The approach that was taken was to develop a tablet-based game that would gather user data during game-play and make predictions, based on machine learning models, as to whether a subject may have ADHD or not. A game design specification was created and outsourced to gaming software developers. This was done since the game development itself was not part of the scope of the study and to ensure that a high quality game would be delivered.

The beta-testing phase included 30 subjects, where the ADHD diagnosis was given by an experienced paediatrician. Initially, the aim of this phase was to develop preliminary models that would be used for the clinical trial that would comprise of 200 subjects. The machine learning model that was implemented was SVM with a linear kernel. Due to the high dimensionality of the dataset, features were extracted through statistical and morphological analysis. Feature selection was then performed in order to have the most representative feature subset. Due to the small size of the dataset, leave-one-out cross-validation was chosen to determine the generalization error of the clas-

sifier, as well as to tune the regularization parameter. The feature set that was chosen consisted of 21 features that were selected using sequential forward selection. This feature selection method outperformed the other 3 methods that were used. The selected features included 11 of the game-play features and 10 of the features extracted from the accelerometer.

Performance metrics of the classifier revealed that although the test and LOOCV accuracies were good (85.7% and 83.5% respectively) care had to be taken when selecting a classifier as being optimal. Important metrics, especially for diagnosing/screening conditions included specificity and sensitivity, which relate to how well a classifier correctly rules out negatives and correctly includes positives. From a screening point of view, the penalty is not as large as for diagnosis, but it is most desirable to have very high sensitivity and acceptable to high specificity. It was seen that the sensitivity was 75% while the specificity was 100%. The sensitivity was seen as low, while the specificity, although being high, was specific to this small dataset and would most likely decrease with a bigger dataset.

Finally, the study that was conducted was able to suggest an answer to the research question that was presented, that is: a person can be screened for ADHD using quantitative methods. It was seen that the classifier showed acceptable results, especially considering that those results were only preliminary. It was demonstrated that, given a data acquisition method, in this case being the game tablet, meaningful data could be extracted and used to build a predictive model. The methods that were used to build the model were based on an extensive literature review, where it was shown successfully how those methods were performed with reliability and repeatability. Therefore, the classifier developed for the study was not novel in itself, but it was the whole design process that was novel.

7.2 Recommendations

The first recommendation is to use a larger sample size, possibly of more than 200. Given the small sample size used in the beta-testing phase, the repeatability and robustness of the SVM model are unknown. The limitation of this is that the results of the study are only indicative of the possibility of developing robust models. Hand-in-hand with the first recommendation is to extract a larger feature set using methods such as mutual information, frequency features and wavelet features.

Due to the complexity of game development, a simple game with minimal features was implemented. Next, it is recommended that a more interactive and complex game be developed, where more features can be extracted and more parameters can be monitored. A more complex implementation would

give a feature set with higher quality and possibly better classifier performance. Furthermore, many studies have shown that the use of multivariate-time-series (MTS) can help accurately classify diseases such as cancer and even ADHD. Such MTS data is found in EEG, ECG and EMG. These could be implemented into the game by placing sensors and electrodes on subjects. Additional physiological markers could be added, such as eye tracking and heart rate.

Finally, this study formed part of a joint project where the tool to be developed was a tool to screen both subtypes of ADHD. While this study pertained to the development of a screening tool for the hyperactivity subtype, the other study dealt with the inattentive subtype. The aim of the two studies was to independently differentiate between ADHD-inattentive and normal and ADHD-hyperactive and normal. These two studies could then be combined in future work to provide for a more robust tool. The tablet-based game would then integrate the two games that were developed for both studies and cover a wider spectrum of ADHD. Furthermore, this integrated tool could provide better insight into factors such as drug effectiveness and quantitative tracking of subject performance. Ultimately, the aim would be to develop a tool that can screen for a wider range of mental disorders that include ADHD, autism and Tourettes. By successfully demonstrating the use of quantitative techniques, this study served as a starting point for further research that can be done in the field of mental disorder diagnosis.

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Appendices

A Ethics

A.1 Ethical Approval Letter

See following page.



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Approved With Stipulations New Application

14-July-2017

Ethics Reference #: M17/05/019

Title: PANDAS: Paediatric Attention-Deficit/Hyperactivity Disorder Application Software

Dear Mr Herve Mwamba,

The **New Application** received on **30-June-2017** was reviewed by members of **Health Research Ethics Committee (HREC) 2** via **expedited** review procedures on **14-July-2017** and was approved with stipulations.

Please note the following information about your approved research protocol:

Protocol Approval Period: **14-July-2017 – 13-July-2018**

The Stipulations of your ethics approval are as follows:

1. **Please list Prof Pieter Fourie, Dr Dawie van der Heever and Ms Rose-Hannah Brown as Collaborating Investigators in Section 4 of the HREC Application Form.**
2. **Please submit a CV and a completed Investigator Declaration Form for Ms Rose-Hannah Brown.**

Please remember to use your protocol number (M17/05/019) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:

Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired.

The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372

Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No. 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki and the South African Medical



Fakulteit Geneeskunde en Gesondheidswetenskappe
Faculty of Medicine and Health Sciences

STELLENBOSCH UNIVERSITY
Health Research Ethics Committee

14 JUL 2017



Afdeling Navorsingsontwikkeling en -Steun • Research Development and Support Division

STELLENBOSCH UNIVERSITEIT
Gesondheidsnavorsing Etyekomitee

Postbus/PO Box 241 • Cape Town 8000 • Suid-Afrika/South Africa
Tel: +27 (0) 21 938 9677



Research Council Guidelines as well as the Guidelines for Ethical Research: Principles, Structures and Processes 2015 (Departement of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Departement of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Departement of Health (healthres@pgwc.gov.za; Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za; Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

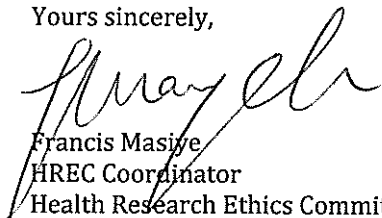
For standard HREC forms and documents, please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Included Documents:

Protocol Synopsis
 Protocol
 Application form
 General Checklist
 Informed Consent Form
 Assent Form
 PANDAS Clinical Trial Process Flow Chart
 Investigator's Declaration P Fourie
 Investigator's Declaration H Mwamba
 Investigator's Declaration R Swarts
 Investigator's Declaration D van der Heever
 CV P Fouries
 CV H Mwamba
 CV R Swarts
 CV D van der Heever

Yours sincerely,



Francis Masiye
 HREC Coordinator
 Health Research Ethics Committee 2



Fakulteit Geneeskunde en Gesondheidswetenskappe
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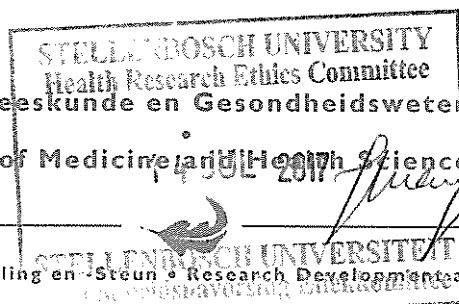
INVESTIGATOR RESPONSIBILITIES Protection of Human Research Participants

Some of the responsibilities investigators have when conducting research involving human participants are listed below:

1. **Conducting the Research:** You are responsible for making sure that the research is conducted according to the HREC approved research protocol. You are also responsible for the actions of all your co-investigators and research staff involved with this research.
2. **Participant Enrolment:** You may not recruit or enrol participants prior to the HREC approval date or after the expiration date of HREC approval. All recruitment materials for any form of media must be approved by the HREC prior to their use. If you need to recruit more participants than was noted in your HREC approval letter, you must submit an amendment requesting an increase in the number of participants.
3. **Informed Consent:** You are responsible for obtaining and documenting effective informed consent using **only** the HREC approved consent documents, and for ensuring that no human participants are involved in research prior to obtaining their informed consent. Please give all participants copies of the signed consent documents. Keep the originals in your secured research files for at least fifteen (15) years.
4. **Continuing Review:** The HREC must review and approve all HREC approved research protocols at intervals appropriate to the degree of risk but not less than once per year. There is **no grace period**. Prior to the date on which the HREC approval of the research expires, **it is your responsibility to submit the continuing review report in a timely fashion to ensure a lapse in HREC approval does not occur**. If HREC approval of your research lapses, you must stop new participant enrolment, and contact the HREC Office immediately.
5. **Amendments and Changes:** If you wish to amend or change any aspect of your research (such as research design, interventions or procedures, number of participants, participant population, informed consent document, instruments, surveys or recruiting material), you must submit the amendment to the HREC for review using the current Amendment Form. You **may not initiate** any amendments or changes to your research without first obtaining written HREC review and approval. The **only exception** is when it is necessary to eliminate apparent immediate hazards to participants and the HREC should be immediately informed of this necessity.
6. **Adverse or Unanticipated Events:** Any serious adverse events, participant complaints, and all unanticipated problems that involve risks to participants or others, as well as any research-related injuries, occurring at this institution or at other performance sites must be reported to the HREC within **five (5) days** of discovery of the incident. You must also report any instances of serious or continuing problems, or non-compliance with the HREC's requirements for protecting human research participants. The only exception to this policy is that the death of a research participant must be reported in accordance with the Stellenbosch University Health Research Ethics Committee Standard Operating Procedures
www.sun25.sun.ac.za/portal/page/portal/Health_Sciences/English/Centres%20and%20Institutions/Research_Development_Support/Ethics/Application_package. All reportable events should be submitted to the HREC using the Serious Adverse Event Report Form.
7. **Research Record Keeping:** You must keep the following research-related records, at a minimum, in a secure location for a minimum of fifteen years; the HREC approved research protocol and all amendments; all informed consent documents; recruiting materials; continuing review reports; adverse or unanticipated events; and all correspondence from the HREC.
8. **Reports to the MCC and Sponsor:** When you submit the required annual report to the MCC or you submit a required report to your Sponsor, you must provide a copy of that report to the HREC. You may submit the report at the time of continuing HREC review.
9. **Provisions of Emergency Medical Care:** When a physician provides emergency medical care to a participant without prior HREC review and approval, to the extent permitted by law, such activities will not be recognized as research nor will the data obtained by any of such activities be used in support of research.
10. **Final Reports:** When you have completed (no further participant enrolment, interactions, interventions or data analysis) or stopped work on your research, you must submit a Final Report to the HREC.
11. **On-Site Evaluations, MCC Inspections, or Audits:** If you are notified that your research will be reviewed or audited by the MCC, the Sponsor, any other external agency or any internal group, you must inform the HREC immediately of the impending audit/evaluation.



Fakulteit Geneeskunde en Gesondheidswetenskappe
Faculty of Medicine and Health Sciences



Afdeling Navorsingsontwikkeling en Steun • Research Development and Support Division

A.2 Parental Information Leaflet and Consent Form

See following page.

PARENTAL INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:

PANDAS (Paediatric Attention-Deficit/Hyperactivity Disorder Application Software)

REFERENCE NUMBER: M17/05/019

RESEARCHERS NAME(S):

Prof. Pieter Fourie (Primary Investigator and Project Supervisor)

Dr. Dawie Van den Heever (Project Supervisor)

Mr. Hervé Mwamba (Researcher)

Mr. Romano Swarts (Researcher)

Ms. Rose-Hannah Brown (Counselling Psychologist)

ADDRESS:

Department of Mechanical and Mechatronic Engineering

Room 616

C/O Banhoek & Joubert Streets

Stellenbosch

7600

CONTACT NUMBER:

Office: (021) 808 3613

Cell: 082 551 1845 (Prof. Fourie)

083 556 8311 (Dr. Van den Heever)

084 784 2443 (Hervé)

084 041 1209 (Romano)

082 329 1307 (Rose-Hannah Brown)

E-mail: prfourie@sun.ac.za (Prof. Fourie)

dawie@sun.ac.za (Dr. Van den Heever)

hervemwamba279@gmail.com (Hervé)

rswarts@sun.ac.za (Romano)

rose-hannah@mtloaded.co.za (Rose-Hannah Brown)

Introduction

Your child has been invited to take part in a research study conducted by Hervé Mwamba and Romano Swarts, two Biomedical Engineering Masters students from Stellenbosch University. This document serves to give you a thorough overview and explanation of the project. Please take some time to read through the following information.

It is very important that you fully and clearly understand what the research entails, and that you are comfortable with your child participating in the study. It is also important to note that your child's participation is entirely voluntary, and you are free to decline to participate or withdraw from the study at any point before or after commencement. If you decline to participate or choose to withdraw from the study, you and/or your child will not be affected negatively in any way whatsoever.

This study has been approved by the Committee for Human Research at Stellenbosch University and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

Testing for this study will take place at the Cape Gate Therapy Centre which is located at 51 Tanner Street, Brackenfell, 7560, Cape Town.

If anything remains unclear or if you would like to talk to one of the researchers, please feel free to ask the study staff or doctor (Prof. Pieter Fourie) any questions about any part of this project.

What is this study all about?

The purpose of this study is to determine whether a specifically designed tablet game is able to detect whether or not ADHD symptoms are present in an individual. The study will be conducted at the Cape Gate Therapy Centre, where a group of 200 patients will be tested in the study. Game data will then be processed and the diagnostic results will be compared with the patients' clinical diagnoses, if any have been made.

Methodology

Mine Runner

Mine Runner is an activity presented in the PANDA tablet game. The task features a panda on a cart, travelling through a dark mine. Sustained attention will be tested as the speed of the character increases over time and obstacles are introduced. The player is required to make use of a joystick to avoid oncoming obstacles, but the task becomes more difficult as distractions are introduced, attempting to force errors. Overall, the task has been designed to be immersive, attempting to keep the player engaged until the task has been completed.

River Rafting Task (RRT)

The River Rafting Task is a task presented in the PANDAS tablet game. The task features a panda on a float, racing down a turbulent river past sheer cliffs of sharp rock and green vegetation. Reflexes will be tested as the speed of the float increases over time and obstacles are introduced in the form of boulders and fallen trees. The player will have the option to avoid or destroy these obstacles, but the task becomes more difficult as distractions are introduced,

attempting to force errors. Overall, the task has been designed to be captivating (multiple sound and light effects), attempting to keep the player engaged until the task has been completed.

House Building Task (HBT)

The House Building Task is a task presented in the PANDAS tablet game. The task features a panda in need of shelter and having to repair a broken-down house in the forest. The task comes in the form of a puzzle, testing the level of cognitive function and problem solving whilst being immersed in a dense forest. The house will have holes (puzzles to be completed) in each of its four walls before the shelter can be used. Difficulty will increase as more holes are successfully completed (repaired) with the presented puzzle pieces. Overall, the task has been designed to be captivating (multiple sound and visual appeal), attempting to keep the player engaged until the task has been completed.

Other deviations from standard treatment associated with the study

No deviations will occur. Your child will simply be given a tablet on which to play a game. When the game has been completed, the tablet will be returned and the assessment is complete.

Why have you been invited to participate?

For this study, we need to test individuals between ages 4 to 18, as ADHD symptoms are most prominent and generally more easily detectable in these individuals. Your child has been invited to participate as they fall within the specified age range.

What are my responsibilities?

You do not have any responsibilities.

How long will this study take?

If you allow your child to participate in the study, your child will be asked to play a tablet game for a duration of approximately 15 minutes.

Will you benefit from taking part in this research?

Your child will not benefit directly from this project, since the results of the study will not be used in the treatment of your child.

Are there any risks involved in taking part in this research?

The mobile device (tablet) that will be used does not pose any risk to you or your child, unless handled incorrectly.

If you do not agree to take part, what other alternatives do you have?

As already mentioned, participation in this study is entirely voluntary. Any participant can withdraw from the study at any point, at the discretion of the parent or the child. Withdrawal from the study will not affect you or your child negatively in any way.

Who will have access to your medical records?

All information collected will be treated as strictly confidential. Should it be used in a publication or thesis, the identity of the participant will remain anonymous. Only HREC members, the study investigators and sponsors will have direct access to the information collected.

Will you be paid to take part in this study and are there any costs involved?

You will not be paid to take part in the study. Participation in the study is free.

What if something goes wrong?

In the unlikely event that your child is hurt as a result of his/her participation in the study, the supervising paediatrician, Prof. Pieter Fourie, will be informed immediately and will take appropriate steps.

Is there anything else that I should know or do?

You can contact Prof. Pieter Fourie at 082 551 1845 if you have any further queries.

You can contact the Committee for Human Research at (021) 938 9207 if you have any concerns or complaints that have not been adequately addressed by the study staff.

You will receive a copy of this information and consent form for your own records.

Declaration by Participant

By signing below, I agree to take part in a research study entitled, "PANDAS (Paediatric Attention-Deficit/Hyperactivity Disorder Application Software)".

I declare that:

1. I have read (or have been read to) the contents of this document and agree to all information and/or conditions given therein.
2. Ample time has been given to me to ask and/or question the information and/or conditions in this document.
3. All questions that were posed by myself have been answered and I fully comprehend the entirety of this study.
4. I understand the risk involved in this study.
5. I understand that taking part in this study is voluntary and I have not been pressurised to take part.
6. I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
7. I acknowledged that I am a volunteer participating in this study out of free will and have not been forced to do so.

Signed at _____ on _____ 2017.

Signature of Participant _____ Signature of Witness _____

Declaration by Investigator

I, (the investigator), hereby declare that:

1. I have fully explained the information in this document to.
2. I have informed the applicant to the best of my abilities.
3. I have encouraged the applicant to question the risks involved in this study.
4. I have encouraged the applicant to question the information and conditions set out in this document.
5. That I have not forced the applicant to volunteer for the study.

Signed at _____ on _____ 2017.

Signature of Investigator _____ Signature of Witness _____

A.3 Participant Information Leaflet and Assent Form 4-11 y/o

See following page.



PARTICIPANT INFORMATION LEAFLET AND ASSENT FORM



TITLE OF THE RESEARCH PROJECT:

PANDAS (Paediatric Attention-Deficit/Hyperactivity Disorder Application Software)

RESEARCHERS NAME(S):

Prof. Pieter Fourie

Mr. Hervé Mwamba

Ms. Rose-Hannah Brown

Dr. Dawie van den Heever

Mr. Romano Swarts

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084 041 1209 (Romano)
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hervemwamba279@gmail.com (Hervé)
rswarts@sun.ac.za (Romano)
rose-hannah@mtloaded.co.za (Rose-Hannah Brown)

What is RESEARCH?

Research is looking for answers to questions we have. These questions can be about anything. The answers we find make people's lives easier and things work better.

What is this research project all about?

Some children find it hard to concentrate. We have made a tablet game for lots of children to play so that we can see who finds it easy to focus and who does not.

Why have I been invited to take part in this research project?

You are the right age to help us with our project.

Who is doing the research?

Professor Fourie. Hervé and Romano will be helping him.

Where will this study take place?

This study will take place at the Cape Gate Therapy Centre in 51 Tanner Street, Brackenfell, 7560, Cape Town.

How long will this study take?

The tablet game will take about 15 minutes.

What will happen to me in this study?

You will be in a room with one of the researchers. You will then be asked to play a tablet game once.

Can anything bad happen to me?

No, you will only be playing a game on a tablet.

Can anything good happen to me?

Hopefully, you will have fun.

Will anyone know I am in the study?

Only your parents and the researchers will know.

Who can I talk to about the study?

Prof. Pieter Fourie (082 551 1845)
Mr. Hervé Mwamba (084 784 2443)
Ms. Rose-Hannah Brown (082 329 1307)

Dr. Dawie van den Heever (083 556 8311)
Mr. Romano Swarts (084 041 1209)

**What if I do not want to do this?**

You do not have to do anything you do not want to. Even if you want to take part now, you can still change your mind later. You will be allowed to leave at any time.

Do you understand this research study and are you willing to take part in it?

 YES NO

Has the researcher answered all your questions?

 YES NO

Do you understand that you can pull out of the study at any time?

 YES NO

Signature of Child

Date

A.3 Participant Information Leaflet and Assent Form 12-18 y/o

See following page.



PARTICIPANT INFORMATION LEAFLET AND ASSENT FORM



TITLE OF THE RESEARCH PROJECT:

PANDAS (Paediatric Attention-Deficit/Hyperactivity Disorder Application Software)

RESEARCHERS NAME(S):

Prof. Pieter Fourie

Mr. Hervé Mwamba

Ms. Rose-Hannah Brown

Dr. Dawie van den Heever

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hervemwamba279@gmail.com (Hervé)
rswarts@sun.ac.za (Romano)
rose-hannah@mtloaded.co.za (Rose-Hannah Brown)

What is RESEARCH?

Research is something we do to gain new knowledge about the way things (and people) work. We use research projects or studies to help us find out more about a disorder, disease or illness. Research also helps us to find better ways of helping, treating and caring for children who need it.

What is this research project all about?

This research project aims to help find a better way to tell the difference between children who have difficulty paying attention and children who do not. The project will use a tablet game to do this.

Why have I been invited to take part in this research project?

The easiest stage to find out whether someone has a problem paying attention is between the ages of 4 and 18.

Who is doing the research?

Professor Fourie, Mr. Hervé Mwamba and Mr. Romano Swarts will be doing the research. Hervé and Romano are both Masters students at Stellenbosch University, trying to find a better way to tell the difference between young people who have difficulty paying attention and those who do not.

Where will this study take place?

This study will take place at the Cape Gate Therapy Centre which is located at 51 Tanner Street, Brackenfell, 7560, Cape Town.

How long will this study take?

The tablet game will take about 15 minutes.

What will happen to me in this study?

You will be in a room with one of the researchers where you will be asked to play a tablet game once. This will be enough to help us complete our study.

Can anything bad happen to me?

There is no known harm that can come to you.

Can anything good happen to me?

There are no known benefits to taking part in this study.

Will anyone know I am in the study?

Only your parents and the researchers will know. Your personal information and tablet game results will be kept secret. Information from the game will only be given to the research staff.

Who can I talk to about the study?

Prof. Pieter Fourie (082 551 1845)
Mr. Hervé Mwamba (084 784 2443)
Ms. Rose-Hannah Brown (082 329 1307)

Dr. Dawie van den Heever (083 556 8311)
Mr. Romano Swarts (084 041 1209)

**What if I do not want to do this?**

If you are not comfortable taking part in the study, you do not have to take part. We want you to know that you can stop participating in this study at any time.

Do you understand this research study and are you willing to take part in it?

 YES NO

Has the researcher answered all your questions?

 YES NO

Do you understand that you can pull out of the study at any time?

 YES NO

Signature of Child

Date

B DSM-5 Criteria

See following page.



Attention-Deficit/Hyperactivity Disorder (ADHD)

314.0X (F90.X)

Cecil R. Reynolds, PhD
Randy W. Kamphaus, PhD

PEARSON

Attention-Deficit/Hyperactivity Disorder (ADHD)**314.0X (F90.X)****A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):**

- 1. Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

- a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
- b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
- c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
- d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
- e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
- f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
- g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
- h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
- i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

- 2. Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

- a. Often fidgets with or taps hands or feet or squirms in seat.
- b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).

- c. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
- d. Often unable to play or engage in leisure activities quietly.
- e. Is often “on the go,” acting as if “driven by a motor” (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
- f. Often talks excessively.
- g. Often blurts out an answer before a question has been completed (e.g., completes people’s sentences; cannot wait for turn in conversation).
- h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
- i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people’s things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

- B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.**
- C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).**
- D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.**
- E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).**

Specify whether:

314.01 (F90.2) Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.

314.00 (F90.0) Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.

314.01 (F90.1) Predominantly hyperactive/impulsive presentation: If Criterion A2 (hyperactivity-impulsivity) is met but Criterion A1 (inattention) is not met over the past 6 months.

Specify if:

In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:


Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in only minor functional impairments.

Moderate: Symptoms or functional impairment between “mild” and “severe” are present.

Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

C NVIDIA K1 Shield Tablet Datasheet

See following page.



Released 2015, November
 356g, 9.2mm thickness
 Android 5.0, up to 7.0
 16GB storage, microSD card slot

~ 0.3%
512,247 HITS

♥ 45
BECOME A FAN

8.0"
1920x1200 pixels

5MP
Video recorder

2GB RAM
Nvidia Tegra K1

5200mAh
Li-Ion

OPINIONS
COMPARE
PICTURES

NETWORK	Technology	No cellular connectivity	<small>EXPAND ▼</small>
LAUNCH	Announced	2015, November	
	Status	Available. Released 2015, November	
BODY	Dimensions	221 x 126 x 9.2 mm (8.70 x 4.96 x 0.36 in)	
	Weight	356 g (12.56 oz)	
	SIM	No	
		- Stylus	
DISPLAY	Type	IPS LCD capacitive touchscreen, 16M colors	
	Size	8.0 inches, 185.6 cm ² (~66.6% screen-to-body ratio)	
	Resolution	1920 x 1200 pixels, 16:10 ratio (~283 ppi density)	
	Multitouch	Yes	
PLATFORM	OS	Android 5.0 (Lollipop), upgradable to 7.0 (Nougat)	
	Chipset	Nvidia Tegra K1	
	CPU	Quad-core 2.2 GHz Cortex-A15	
	GPU	ULP GeForce Kepler (192 cores)	
MEMORY	Card slot	microSD, up to 256 GB (dedicated slot)	
	Internal	16 GB, 2 GB RAM	
MAIN CAMERA	Single	5 MP, AF	
	Features	HDR	
	Video	Yes	
SELFIE CAMERA	Single	5 MP	
	Features	HDR	
	Video		
SOUND	Alert types	Vibration; MP3, WAV ringtones	
	Loudspeaker	Yes, with stereo speakers	
	3.5mm jack	Yes	
		- Dual bass reflex port	
COMMS	WLAN	Wi-Fi 802.11 a/b/g/n, dual-band	
	Bluetooth	4.0, A2DP, LE	
	GPS	Yes, with A-GPS, GLONASS	
	Radio	No	
	USB	microUSB 2.0	
FEATURES	Sensors	Accelerometer, gyro, compass	
	Messaging	Email, Push Email, IM	
	Browser	HTML5	
		- HDMI port	
		- MP4/H.264 player	
		- MP3/WAV/eAAC+ player	
		- Photo/video editor	
		- Document viewer	
BATTERY		Non-removable Li-Ion 5200 mAh battery (19.75 Wh)	