Thesis Draft report

Objectifying the SARA score

Mahsa Behzadi

Table of Contents

Preface

This document has been prepared in partial fulfilment of the requirement for the subject: Master Sensor System engineering, Hanze University of Groningen in the academic year 2015-2016.

The purpose of this project is to provide objective scale for ataxia disease. The first symptom of this disease is disorders in coordination and balance. Measuring movement of the patients of ataxia will provide reliable information to define an accurate objective scale for severity and type of this disease. This document discusses about ataxia, current situation and desired situation. Theoretical and situational analysis of movements in these patients, at the end we will discuss about our research design based on the theoretical and situational analysis that has been mentioned.

A group of students participate in this project,

1. Mahsa Behzadi: Master sensor system engineering.
2. Adriella van der veen: Master Movements Disorders.
3. Benedikt Ritz: Neurology master student.

This project is supervised by Prof. Natasha Maurits and PHD researcher Octavia Martinez Manzanera.

The project has been started since Feb 2016 and will be continued after my internship with help of other interns. In addition to the knowledge that I have learned through my Master Courses in Sensor System Engineering and Programming in Hanze University of Groningen, the previous researches of Prof. Maurits and PHD researcher Octavia Manzanera helped me enormously through this project.

Introduction

Ataxia originally is a Greek word by the meaning of confusion and absence of order (1). This disease is defined as gait imbalance and motor incoordination (2). Ataxia which is one of the consequences of cerebellum dysfunction, the part of nervous system that controls the balance is affected (2). The cerebellum has a major role in modulating movement as well as the control of muscular tone, coordination, voluntary movements, control of posture and gait, speech and eye movement (3).

The first symptom of ataxia is usually in balance and coordination that can affect meaningful activities such as speech, gait and gaze (4). In healthy people voluntary movements are smooth because of the correct coordination of muscles, however in ataxia patients, due to motor control dysfunction and incorrect motor responses and poor balance and coordination, voluntary movements cannot be performed appropriately (5). Ataxia can affect daily activities performances, and the neuropathy of the advanced ataxia leads to loss of position and vibration sensation, disorders of speech, disorders of limb movement and disorders of eye movement(6).

There is a variety of ataxia disease that has different cause including genetic and non-genetic forms (7). Ataxia is one of the principle symptoms of a group of hereditary neurogenerative disorders such as Friedreich ataxia, autosomal dominant spinocerebellar ataxia (SCA), ataxia telangiectasia and well known regarding of one of the sign and symptoms which have a possibility to occur in some common neurological diseases such as stroke. Although, the cause of this disease is still unknown for some cases (8) (9). Symptoms, severity and the time of onset of this disease are different bases on the type of ataxia (8).

The aim of this project is to provide an objective assessment that researchers, clinician, and neurologist can use to improve their analysis and diagnosis. In this project, we are attempting to record movements of ataxia patients accurately with Internal Measurements Units, to provide reliable information on dysfunctions and disorders of movements. Based on the recorded data, extracting features and analysis we expect to create an objective and continuous scale for ataxia

that provides reliable information about the type and severity of ataxia and also helps to improve the diagnosis of this disease.

Current situation

At the present, there are over 100 clinical and laboratory studies developing a reliable scale for ataxia. The terms of cerebellar ataxia have a broad range of disorders. This field has challenged by recent advances in neuroimaging and translational progress. Recent studies in molecular biology and genetics provide availability of several blood tests and genetic tests (10) (11).

Recent researches show that ataxia usually has an onset in adulthood, and some cases patient may not realize the disease and remain clinically healthy until their 60s. Dominant ataxia usually begins in the 30s even later also Friedreichs ataxia often has an onset in adulthood. In Hereditary ataxia, due to their hereditary nature, the pathogenic process often start early in life. However it takes many years to process and in some cases, patients remain healthy until their 20s, 30s even 70s (12) (13) (14).

Early-onset ataxia (EOA) are a group of rare inherited disorders showing sign and symptoms of ataxia before 25th years of life. The onset of ataxia in early childhood can lead to weakening for children since they are at the level of developing and learning motor capabilities (15). The exact disease onset remains unclear most of the time (16). The severity of ataxia and its effects depend on the type of ataxia, the age at onset and other factors that are not well understood yet. One of the most important aims of diagnosis and monitoring ataxia is to classify the type of ataxia and severity of this disease (17).The Scale for Assessment and Rating of Ataxia (SARA) is known for a clinical gold standard for recognizing the severity of this disease. This scale measures ataxia in gait, kinetic function and speech and eye movement (17).

There are many examinations and test to identifying ataxia symptoms from other movement disorders (18). Also, there are several commonly used rating scales for ataxia such as the international cooperative ataxia rating scale (ICARS), which has 19 items for scoring ataxia.

Ranging each item is from 0 (no ataxia) to 100 (most severe ataxia). This scale is commonly used for clinical evaluation and is composed of clinical sub scores involving speech, limb, and gait (19). The SARA, which Schmitz-Hubsch presented in 2004, is another tool for assessing ataxia. It has eight items with total scores ranging from 0 (no ataxia) to 40 (most severe ataxia). Scores for the eight items range as follows: no ataxia, 1: gait (0-8 points), 2: stance (0-6 points), 3: sitting (0-4 points), 4: speech disturbance (0-6 points), 5: finger Chase (0-4 points), 6: nose-finger test (0-4 points), 7: fast alternating hand movement (0-4 points), 8: heel-shin slide (0-4 points), and 40: severe ataxia. For motor activities of the four extremities (items 5-8), assessments are performed bilaterally, and the mean values are used to obtain the total score (17). SARA and ICARS have been the best studied and validated scales so far, and their reliability sustains their use. SARA is simpler and faster for patients to execute than ICARS; moreover, dismissed items of ICARS can cause problem and inaccuracy. SARA may thus be a better choice (20)

Since EOA often presents as a combined disorder in children that can lead to a low inter-observer agreement, the uniform assessment of SARA scores can be difficult. Also, age-related maturation of the brain and nervous system can result in false ataxia score (21). Finger to nose test are Coordination-specific tasks inducing intention tremor and finger chase test are some of the dysmetria tests (24). Martinez-Manzanera et al. showed that digital quantification of a specific subscale (finger-to-nose) is possible in children. Furthermore, these authors indicated that the quantified parameters are helpful to distinguish between children suffering from ataxia and other conditions causing impaired motor coordination (such as developmental coordination disorder). Quantification and measurements of the finger-chase test of the SARA have not yet been attempted. These studies resulted in a wide variety of measurement methods for ataxia assessments to be extended in coming years (24).

Desired situation

Many researchers, biologists and clinician experience difficulties in analyzing of movement disorders, since the clinical diagnosis of types of ataxia is usually complicated by a salient overlap of phenotypes between genetic types and given the wide range of cerebellum affected disorders. Various diagnostic tools have been developed in the past decade. However, they are still limited to laboratories, with deficiency of standardization (23). All rating scales that are widely used for ataxia are subjective and inaccurate. Some of the small changes in movements cannot be detected by clinicians, therefore, the reliability of detection is limited and the results depend on clinician judgments can vary. Though, computerized systems are highly reliable, they are costly systems which require working within the laboratory environment (23).

Aim of this study

The goal of this project is to create a reliable objective model to score ataxia severity. Patient's movement will be recorded by eight inertial measurement units that are attached to different parts of the body. This small, harmless and light IMUs can provide reliable information about patient's movement without any risk to the patients and difficulty to perform tasks. IMUs are easy to use, and it provides reliable and accurate information on movement performance. Movement performance will also be evaluated by neurologists, the result will consist of a model that scores a patient movement performance as similar as the neurologist concerning mean square error. Cross-validation will be used to determine the expected error on new data. This objective model can be utilized in any clinical environment. We aim to provide an objective assessment for neurologists, clinician and researchers to improve their analysis and diagnosis.

My part in the study

My first part of this project is to record reliable data from patient's movement with IMUs. Recording process starts with calibration of sensors, then recording movements after installation of sensors on patient's body and at last importing data from sensors to computer for analysis. The other role of me in this project is to analyze recorded data of gait movements in patients with ataxia and healthy people to provide information about gait cycles. One of the most important roles in this project is to extract features from the information of the gait cycle of the patients and healthy people. Several features will be extracted to analysis the differences and similarities of these signals based on the theories on gait cycle and gait dysfunction and observation of individual signals. After applying regression, we identify certain important features for gait movements and then patients and healthy people will be classify based on these features. This classification can also provide information to score the severity of this disease in patients.

Situational &Theoretical analysis

One of the aims of current studies and investigations in ataxia is to identify the fundamental problems (24). Due to the identification of these key problems researches on cerebellar and spinal cord functions has increased dramatically during last decade. New ideas about the role and effect of different parts of nervous system and motor control have been suggested. These ideas are based on the involvement of these parts of nervous system and brain in timing and sensory system (25).

In cerebellar ataxia, effect on the patient depends on which of the areas of the brain are lesioned (25), which can happen on one or both side. Patient's balance and eye movement will be disturbed if the vestibulocerebellum is affected. Therefore, patients maintaining balance during stand test is difficult. Unusual gait changes can be seen in patients with Spinocerebellum dysfunction. Spinocerebellar is responsible for controlling limb movements. If cerebrocerebellum is affected, the patient will have difficulties for executing voluntary movements such as head movements, eye movements, hand movements, etc. Speech is also affected in cerebrocerebellum dysfunction and variety of rhythm and volume can be seen in these patients (26). In patients with

sensory ataxia, difficulties in gait is one of the important symptoms, heel striking for this patients are hard when they touch the ground. Also, it can be difficult to execute smooth voluntary coordinated movements for these patients (27). Inherited ataxia is caused by a genetic fault. Non-inherited ataxia also can develop in some conditions such as alcohol abuse, drug abuse, head injury, brain surgery and stroke (28).

Different type of the central lesion of the nervous system can cause the type and severity of ataxia regarding of the site of the lesion such as cerebellar when lesion is in the cerebellum, sensory if in the dorsal spinal cord, and vestibular if in the vestibular system. Ataxia can also be symptoms of infection (29). Some of the characteristics of these disturbances in coordination and movements has been explained by the following theories:

Eye movement disorders:

The role of the cerebellum is significant not only to ensure the calibration of the eye movement system and eye stability. But it is mainly for achieving smoothness of saccadic eye movement, smoothness pursuit and vergence and eye gaze fixation (25). Numbers of cerebellar structures control eye movements and gaze fixation such as fastingius nucleus and modulus. Analyzing eye movements provide information to the clinician that can help for identifying the parts involved in brain dysfunction (25).

Speech disorders:

Speech is one of the highly complex processes of human; this process includes estimated 80 muscles (pair and not pair) to realize rapid, smooth and highly coordinated movements. This movement should be accurately synchronized with the respiratory system. Producing each second of speech requires estimated 1400 motor command (30). One of the neural networks that are involved in aiding humans to speak and creating sound consists of the motor pathway for simple vocalizations such as vocals due to reaction and pain. Another neural network is for more complex forms of motor speech productions like words and meaningful sounds. The role of cerebellar is

critical in this system especially second neural network (31). Speech disorders are caused by delict in timing, sensory acquisition, and disorder of motor predictions in ataxia patients. This can result from the dysfunction of the responsible parts to control speech such as the intermediate cerebellar cortex, the superior prevernal region and dentate cortex (25).

Timing:

Attention to the temporal domain is one of the key elements for understanding cerebellar function. Timing is one of the most important concepts for studies and researches in the cerebellum.There are number of ideas about cerebellum and timing such as the critical role of cerebellum for motor prediction and real-time prediction. Some activities in cerebellar cortex are also critical for temporal decoding (25). Temporal patterning of coordinated movements and their analysis are important features in ataxia due to the inability of patients with ataxia to accurately control the timing needed for their rapid movements (32).

Limb movement disorders:

Limb movements are controlled by the dentate nucleus, the lateral cerebellar cortex and the intermediate cerebellar cortex (25). Also, timing, sensorimotor synchronization, and sensory acquisition are some of the important factors that loss of them result to limb movement disorder (25). There is an overall hypothesis that in patients with cerebellar dysfunction, kinematic factors of movements are effected. Difficulties to recognize the position, direction and velocity and difficulties with predictive motor timing, overall slowness and overshooting/undershooting of actions are common in ataxia patients (33) (34) (35). Usually, in these patients impairment can be observed in initiative and terminative movements (34).

Single-joint movements:

Hypermetria and Hypermetria refer in order to overshoot and undershooting the proposed position. Hypermetria is one of the signs of cerebellum dysfunctions (36). Also, Dymetria may be connected with a kinetic tremor that can lead to slow or moderate speed in visually directed tasks (25). Tremor in kinetic movements in ataxia patients can be apparent especially while maintenance of limbs against gravity (36).

Multi-joint movements:

Impairment in making proper torques in multi-joint movements caused difficulties for ataxia patients to control mechanical actions of dynamic communication forces during this task. The difference in Hand trajectory and timing and velocity of multi-joint tasks can be seen in control and ataxia patients (37).

In the figure below we can observe the difference between hand movement for control and patients in the finger to nose test.

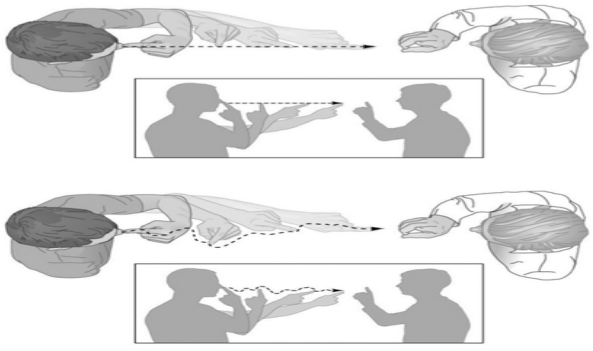

Figure1: finger to nose test has been done in a clinical examination for ataxia. This figure shows ataxia patients hand movement. Tremor can be seen in patient's hand movement. (https://quizlet.com)

The figure below illustrates the change and difference in hand movements for control and patients. In this figure, the difference can be observed. As we can see the dysfunction of different parts of the brain, effects hand movements differently.

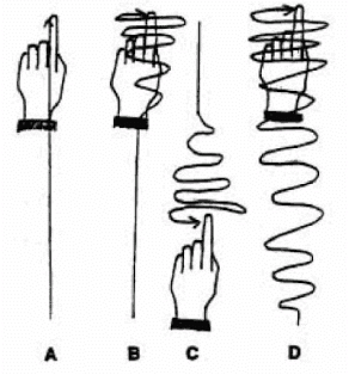

Figure 2: (A) control: smooth and steady movement. (B) Cerebellar hemisphere dysfunction. (C)Parkinsonian: tremor can be seen at the beginning, and it goes smooth as finger reaches the target. (D) Essential tremor: Tremor goes worse as finger reaches the target. (http://2.bp.blogspot.com/-SFewr18T7X4/UA-zGj52YYI/AAAAAAAACWE/hDFUdAcWt4c/s1600/4905.gif)

Impairment of gait/posture:

Stance/gait is under the supervision of the medial and intermediate cerebellum (25). Disorders in the sensory acquisition and motor prediction also timing cause deficit of gait/stance in ataxia patients (25). In general, ataxia can result from damages to sensory systems.The sensory systems are in charge of providing feedback for balance and coordination. Problems with sensory systems can lead disabilities in walking.

Many motor systems should work properly to maintain balance and respond to changing of coordination and environment while walking (38), which is the reason sensory systems are having an important role for gait cycle. For normal gait, the motor system responsible is also responsible for the strength of muscles and coordination, muscle tone and postures. Gait examination is done by two tasks: a) normal locomotion, b) tandem gait. Figure 3,illustrates more variability in movements in patients compare to control (39). Disturbed interlimb coordination of movement can also be seen in figure 3.

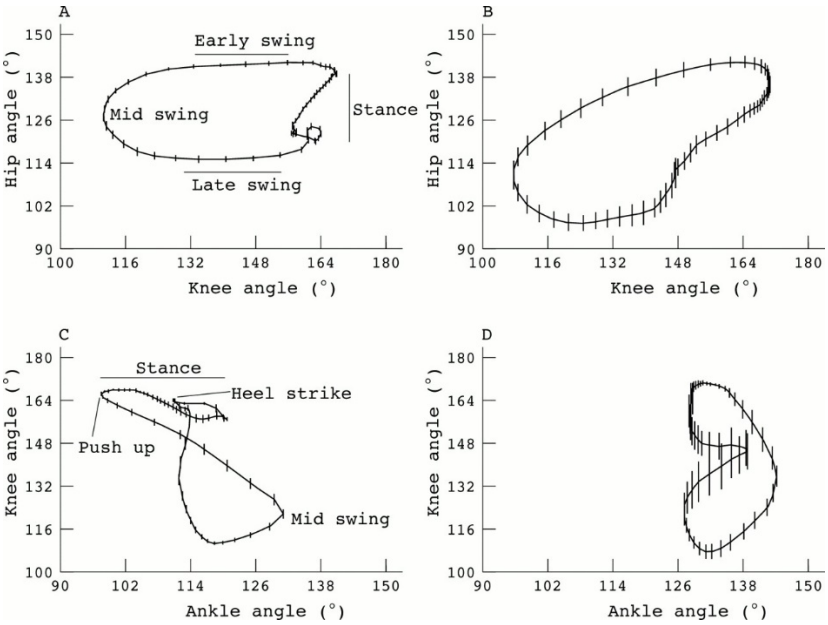

Figure 3: Angle-angle plots for hip-knee joint movements (A, B) and knee-ankle joint movements (C, D). (A, C) Healthy control; (B, D) patients with cerebellar disease (CD). Typical phases of the walking cycle are indicated for the healthy subject. (39)

Some of the differences of gait cycle between cerebellar and control subjects were studied ,the differences are shown in the figure below.

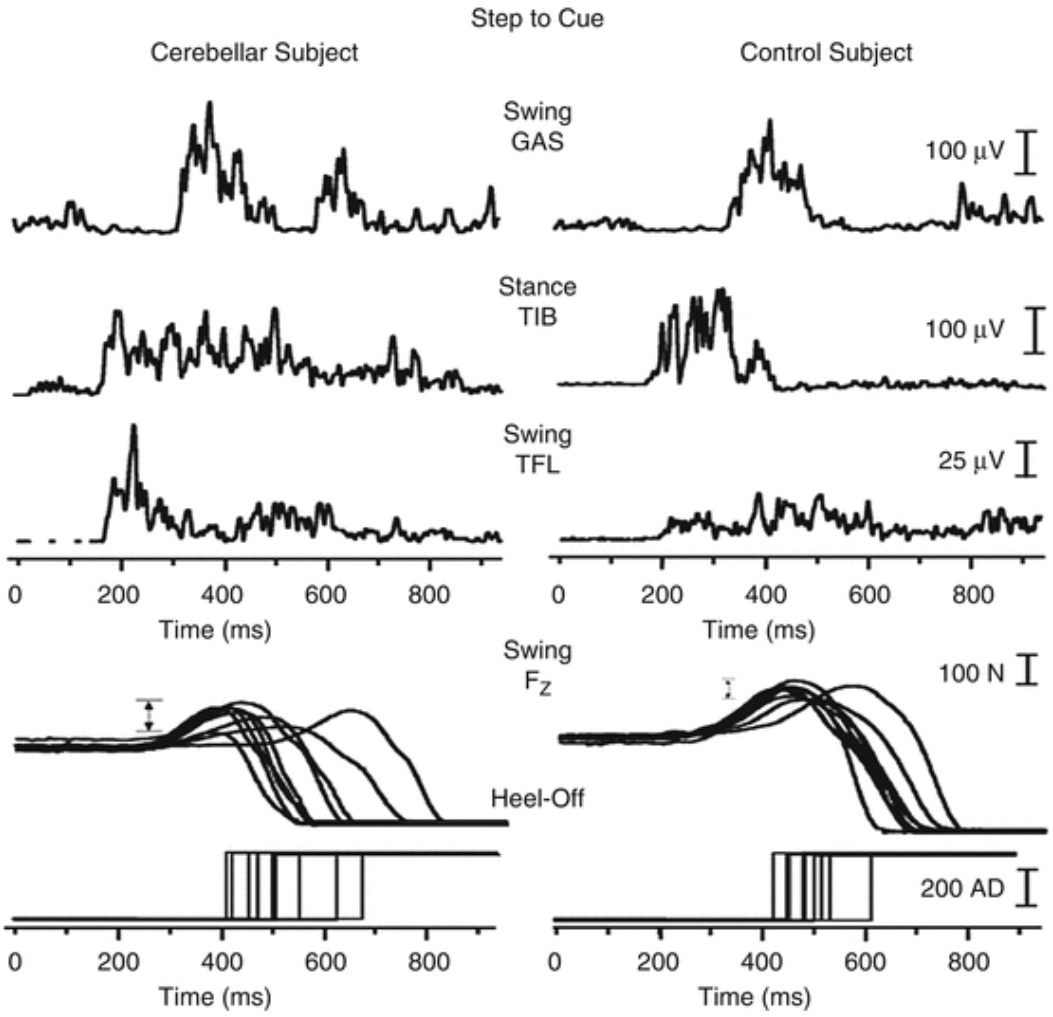

Figure 4: Difference between tandem gait in control and patients. Correct placement of food is critical for tandem movements. In control patients position of heels should be exactly same. As we can observe in patients with ataxia variability in steps are increased that can make difficulties to realizing the ideal path, another difference can be seen in some missteps. Missteps for ataxia patients are far more than control. The pattern of movements in control also is fixed however this pattern is irregular for patients (39).

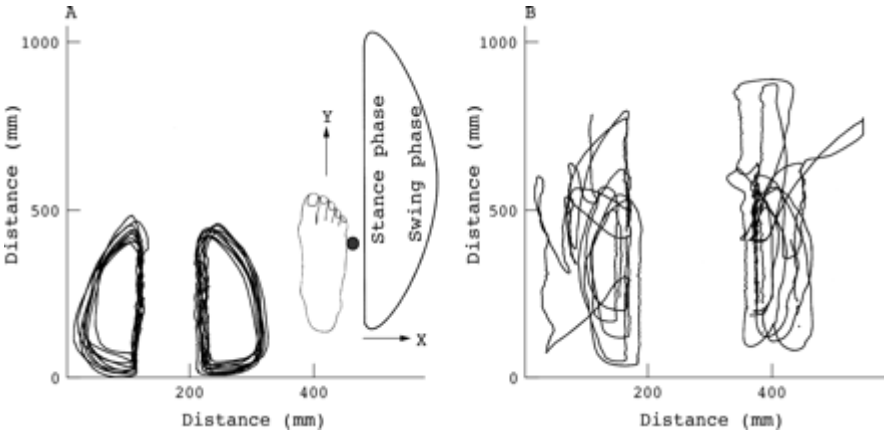

Figure5: continuous tracking of tandem gait for over 20 seconds on the treadmill for control (A) and patients (B)

Beside of the low population frequency of ataxia, unavailability of a reliable biomarkers for assessment of ataxia is the main reason for a lack of treatment for ataxia (40). Based on the neurological examination of characteristics explained above scales for ataxia have been created and used such as Scale for the Assessment and Rating of Ataxia (SARA) and International Cooperative Ataxia Rating Scale (ICARS).Based on the advantages of SARA to ICARS, SARA test remains the clinical gold standard for ataxia and have been widely used (41). SARA test is easy for patients to accomplish and also consume less time than ICARS. SARA scale consists of 8 tests, kinetic function tests (item 5 to 8) are rated separately for the right and left the side. Total score range is from 0 assigned to no ataxia to 40 assigned to most severe ataxia.

Gait (score 0 to 8)

Stance (0 to 6)

Sitting (0 to 4)

Speech disturbances (0 to 6)

Finger chase (0 to 4)

Finger to nose (0 to 4)

Fast alternating hand movements (0 to 4)

Heel-shin slide (0 to 4)

During SARA scale examination, abnormalities and difficulties of the patient are obvious. In kinetic tasks, for example, when ataxia patient has to point a target, uncertainty and less accuracy, regular tremor and slow movements can be seen. Also, overshooting and undershooting target can happen in these tasks (42). Gait/stance task also, can result in difficulties of the patient in maintaining balance and coordination. Abnormality in gait movements is common symptoms in ataxia patients. Accurate monitoring of these functions and limitation of patients in executing them can determine necessary information about type and severity of ataxia (42).

A Wide range of studies have been done on ataxia, however the neurological examinations usually are not sufficiently sensitive to detect short-term interval changes and small changes in muscles coordination (42). Due to lack of accuracy, the SARA score changed per year in some studies (43).There is a growing need for a sensitive and objective method of assessment of ataxia for more accurate information, monitoring and diagnosis of ataxia and also for identifying the symptoms and severity of ataxia (44). Digital quantification of sub-scores of SARA can provide helpful information and more accurately to determine the severity of the disease. Therefore, quantification of the subscale of SARA task can be suitable to detect small changes and also measuring repeated task to achieve chronological changes. Quantification of this functions and limitation of patients for executing them will provide appropriate and more reliable information regarding this disease and the severity of the disease.

Hypothesis:

Are changes in the SARA motor scores (gait and kinetics) quantifiable by automatic, digital quantification?

In the perspective of the above, we hypothesize that quantification of the SARA gait, finger-to-nose, and finger-chase subscales could help to provide a standard clinical instrument for reliable and reproducible SARA assessment (from childhood- to adulthood), allowing for longitudinal follow-up of EOA patients and good quality data entry in international databases. According to provided information, we hypothesize that this assessment could help us to predict the SARA score of the patients and classify patients with different type and severity of ataxia. In EOA patients (with clinically pre-assessed finger-to-nose, finger-chase, and walking subscales), therefore, we aim to extend the above study by quantifying and comparing SARA outcomes across the full range of clinically assessable scores, including children as well as adults.

Conceptual model

Eight tests of SARA scale can rate the symptoms of ataxia and severity of this disease. However, as mentioned before this examination have been done by clinicians. Small changes and disturbances in the execution of these tasks cannot be detected by naked eyes of clinicians. Gait abnormality is one of the most noticeable symptoms of ataxia. However, quantitative studies around this topic are rare. Limb movements can also provide sufficient information about severity and type of ataxia. Extracting three-dimensional position of an effector while the patient is executing the task is critical for accurate motor control. This information is usually important for limbs to specify its state to the nervous system and brain (25).

Objective measurements of different tasks of SARA scale are based on the use of IMU devices to detect and measure various parameters regarding the main features. Installing small internal measuring units on patient's body to detect changes and movements of certain tasks can help to provide accurate information about abnormality in these patients. The difference of the

value of these features in control and patients will be compared. IMU units are small, light and comfortable to wear. Therefore, one of the advantages of using IMU devices is they don't interfere with the patient's movement. The help of triaxial accelerometers, for quantitative analysis of motor function, has been showed in some studies. An IMU device is a small and light device that is not stressful for the patient (41). Tasks to measure with IMU devices are as following:

Gait/stance: Different gait parameters will measure such as velocity, step length, step width, step height, cadence, foot angle, stance, swing, missteps, walking pattern and gait cycle.

Finger to nose and Finger chasing: In these test velocity, overall slowness, trajectory, pattern, single joint and multi-joint analysis (time, torques) will be measured

Diadochokinesia: In this test pattern and lethargy, coordination is necessary to be measured.

Research design

Participants

In total sixty participants joined in this study, thirty ataxia patients(examined by neurologists) and thirty controls. Age, severity and gender of the participants vary . Recording continued to the end of the project to achieve more reliable data and more population frequency. All participants were asked to execute SARA scale task. Patients were invited to participant in this study after their checkup routine by their neurologist. In this project, movements were recorded with IMU devices. IMUs will be installed on patient's body to record the movement of certain parts of the body. Installation of IMU devices is easy and non-invasive. The research was performed according to the research and integrity codes of the University Medical Center Groningen (UMCG). No medical ethical approval was necessary, according to the Medical Ethical Committee of the UMCG, because the measurements belonged to standard patient care. Both patients and controls were asked to sign a form of consent before recording process. seven patients were unable

to perform the gait task due to the severity of gait dysfunction. Three patients were using help during gait tasks.

Apparatus

Calibration of sensors was done on windows 10 laptop using shimmer 9DoF calibration V2.8 software. Synchronization of six sensors were done using multi-charger (shimmer, Dublin, Irland).

Configuration and exporting the data of sensors were done using shimmerLogV0.9 software. The data analysis was run on a Windows 10 PC. The program to present the feature selection for data analysis was written in matlab2014 and the program to present the regression and present the result of data analysis was written in python2011. Eight 9 Degree of freedom sensors (shimmer3 from shimmer, Dublin, Ireland)

Material and Procedure

The recording process started with calibration of sensors. Eight shimmer3 and three shimmer2 were calibrated before each recording using the provided software shimmer 9Dof Calibration v2.5. Each IMU device is composed of three accelerometers, three gyroscopes, and three magnetic sensors. However, magnetic measurements are out of the scope of this project. Accelerometers are orthogonally aligned and measured linear accelerometer in XYZ directions with the sensitivity of 4G. Angular velocity along XYZ axis also measured by three orthogonally aligned gyroscope with sensitivity 500/s. All sensors were sampled at 250hz.

For synchronization of data of all sensors(shimmer3), the internal clock of six sensors were reset to zero by placing the sensors in the multi charger(shimmer, Dublin, Ireland) and pressing the reset button on the charger for all sensors at a time. Due to the inability of synchronization for

more than six sensors, two of the sensors were synchronized separately and the time difference between synchronization was recorded. However, their data excluded from the further data analysis in the current study.

Gait task

After synchronization of all sensors and pressing the record button for each, sensors were attached by elastic straps on different parts of patient's body to detect movements during performing gait/stance and posture task. Each sensors includes an internal SD-card to store the signal, and related timestamps of internal clock (32 kHz).

These sensors were connected to:

- Trunk (sternum): Some of the critical parameters of gait cycle can be obtained from the trunk acceleration data. These parameters are such as the duration of single stride cycle, identification of left and right steps, step length and walking velocity (43).
- Low back (L3 segment of lumbar spinal): L3-L4 vertebrae is the center of the mass of the human body during stance. This segment can detect anteroposterior (AP), vertical (V) and mediolateral movements of the whole body during walking.
- Both thighs (midpoint femur frontal)
- Both shanks (2 cm above malleolus lateralis)
- Both hands

All participants were asked to remove their shoes while performing gait tasks of SARA. All participants were instructed to walk along a walking path for proximal 20 steps, turn and walk back to the starting location at their own preferred and comfortable speed. This task was recorded three or four times if possible to achieve more reliable data. Seven patients were unable to perform the gait task due to severity of gait and also three patients were using help during performance of these tasks.

After recording, the raw signal was transferred to a computer using ShimmerLog v0.16 application. Preprocessing had to be done after recording to calibrate data and to specify the beginning time and end of each task for further analysis.

Finger to nose and finger chasing tasks:

Three IMU devices (shimmer2, Dublib,irland) were attached to participant's upper arm, lower arm and finger by elastic straps for finger chasing and finger to nose task. This task was executed for both left and right hand for all participants.

During finger to nose and finger chasing task, three-dimensional movements of each sensor were recorded and observation of the three-dimensional movements at the same time as patients are executing the task via LabVIEW was possible. For more reliable data, patients were asked to perform finger to nose and finger chasing tasks on touch screen laptop. These tasks were designed to show several points on the screen with a particular location. After patient touching the screen the location of the point and place of that patient press were recorded and the next point appeared. The further analysis of finger to nose and finger chasing is out of the scope of this project.

Some of the other tasks such as speech, eye movements and heel-shin were observed by a clinician. Furthermore, all tasks of SARA scale were recorded on camera for further neurological analysis and evaluation.

Data analysis

Video protocol

Video protocol were done for each participant after recording and it consists of start/end time for each task of SARA. The start/end time are based on the recorded video during process and timestamps were selected according to reset time of internal clocks for sensors (1-6) on multi-charger.

Preprocessing

At first, Signals from sensors attached to arms and signals from manometers were extracted from raw data. Since not recorded data from the whole recording process, were useful, Therefore identification of the approximate start/end time of each SARA task had to be done. According to the video protocol for each participant, start and end timestamps of each task was estimated approximately. For more accuracy signals were observed and magnitude changes of signals were selected in the range of estimated timestamps.

After task selection, by matching the timestamps of internal clocks of all sensors, synchronization of all data were possible. In recording sensors were attached at body parts in same orientation. However for more accuracy calibration was performed. Calibration was performed the way that while participant is standing still y-axis represents upward, x axis represents sideward and the z-axis represents forward.

Gait segmentation

After pre-processing, for each participant a total of 36 time series including six strides were obtained from six sensor locations, three axes (X,Y,Z) and two sensor types (accelerometer and gyroscope). For finding gait characteristics, assessing single stride is important. Each stride has defined as a movement of a single limb from heel strike to the next heel strike event. In this project strides were separated from left heel strike events.

Strides events were identified by using the algorithm for extraction of heel strikes and toe-offs from gait accelerometry signals.(44) .

Data From the tri-axial accelerometer sensor attached to the l3 segment of the lumbar spine were used for this algorithm. Tri-axial accelerometer detect the participant's body movements along medial-lateral (ML), vertical (V) and anterior-posterior (AP) axes.

Algorithm

The algorithm has three stages that are as following;

Identify events of interest

In this step identification of the maximum change of acceleration (local maxima in v direction) as the potential location of events has been done. For identifying events of interest three steps had to be done. Firstly removing artifacts due to gravity, by excluding the mean from the signal. Secondly excluding gait-unrelated artifacts, by median filtering. At the end for reducing the variability in groups and unit variance of combined signal per sensor type, amplitude normalization was applied.

Since stance phase in each stride has been estimated 0.70 seconds, consecutive local maxima in the v direction signal, have to be at least half of the stance phase time apart from each other. This step was performed using Matlab 2014 script based on the algorithm. In this part, all proposed

peaks from the algorithm were provided, and manually selection and modification of more optimal points were possible.

Identify toe-off events for both feet

The purpose of this step is to determine the actual toe-off events for both feet. According to the algorithm, double stance phase of each stride were assumed to lasts for about 15% of the whole stride duration. Therefore, toe-off events are local minima that happened in the range of 0.15 seconds after each point of interest. For distinguishing the left and right toe-off events, the mean value of the first 10ms of the acceleration in ML direction was used. The positive mean value represents that, participant's first step was with the right foot, and negative mean value represents that, the first step of the participant was with the left foot. This step was also performed using matlab2014 script that provides us an automatic selection of right and left toe-off events. In this part modification and selection of points were possible for more accuracy.

Identify heel-strike events for both feet:

After identifying the gait events, left heel strike was selected to separate the strides in each walk event. A total number of 52 walks for thirteen controls and 56 walks for sixteen patients were selected from the data. The gait segmentation was not possible for six of patients due to unsymmetrical walking signal. Number of strides in each walk event for control participants was varied from 7 to 24 .this variety for patients was between 6 to 18 strides per walk.

Sub_research question:

RQ: Are changes in the motor score (gait) detectable?

Ho: changes in motor score (gait) are not detectable

Ha: changes in motor score (gait) are detectable

Extracting features from Average signal of all controls

To answer the sub-research question, signals for controls were analyzed to extract repetitive features. Later the extracted features from control subjects and patients were compared to examine the detection of gait characteristics change. The purpose of this step is to obtain a visualization of the average individual stride signal of all controls and define possible data-driven features. This step was performed by matlab2014 script.

All individual stride signals were selected from 52 walks (controls) for each sensor. The time-normalized average signal was selected from 579 single stride signal for each sensor. For each averaged signal, patterns that can be used as features were observed. Matlab script was applied to extract possible features from 36 time-normalized average stride signal. These features were such as maximum and minimum amplitude, amplitude differences and time differences between positive peaks/negative peaks, minimum, and maximum amplitude. The amplitude difference between positive peaks to the next negative peak was defined as fall level and amplitude differences between negative

Peak to the next positive peak as rising level. The slope of rising level and fall level and area under the curve were also selected as possible features. In total 14 features were extracted from each average stride signal for 36 sensors.

Due to variety in time stamps range of features, some of the important features were discarded, and the average signal was not sufficiently reliable and accurate representative of data.

Feature extraction from individual stride signals of all controls for 36 sensors

After visualization and selection of possible features for average signals, for more accuracy, visualization of individual stride signals was done. 100 individual stride signals were randomly selected and plotted from 579 stride signal for each sensor. Feature extraction in this part was done by observation of repetitive and prominent feature in randomly selected stride

signals. Four features; Amplitude and sample time of one negative and one positive peak were selected for each individual stride signal of 36 sensors. The range of each positive peak and negative peak were selected based on observation of features in individual stride signals. Defining the constant and prominent feature for number of the sensors were not possible (sensor 6-10-23-27-29-36).Features, were extracted from all the control signals for each sensor based on the defined range.

Feature extraction for patients:

In this part, the proposed feature range for each sensor was applied on patient's data. Features were selected from patient's individual stride signal data.

Feature description

In total feature description for patients and controls are as following;

Type	Number of participants	Number of total walks	Number of single strides	Number of selected features
Control	30	52	579	120*576
Paient	30	56	769	120*769

Regression

Sub-Research Question:

RQ: Do extracted features predict SARA score of the patients?

Ho: Independent variable does not predict the dependent variable.

Ha: Independent variable predicts dependent variable.

Linear regression:

To evaluate the sub-research question, linear regression was applied to examine if features can predict SARA score. Linear regression is a suitable analysis to understand the relation between independent variable, that is the mean of SARA scores from neurologists in the current study and the dependent variable that is features extracted from signals. A Linear relationship between features and SARA score were assumed. Scatterplots were examined to for prudence.

Regression was applied based on the following formula: $y=\beta 1*X+C$.In this formula X represents the features, Y accounts for the SARA Score; C accounts for the constant and β represents regression coefficient(45-46).

Normalization

Normalization was done before regression on features data to avoid misleading information and overweighting. Due to normalization C was equaled to zero and β value were remained consistent and β information were more accurately related to the influence of the features.

Residual sum of squares (RSS) was used to measure the difference between the fitted model and the actual data. The coefficient of determination(R-squared) was also used to report how fit is the data to the predicted model. Linear regression was applied by python 2011.

RQ: Does estimated model predict SARA score for the new patient?

Ho: the estimated model does not predict SARA score for the new patient?

Ha: estimated model predicts SARA score for the new patient?

Cross-validation

The R-squared value has become standard for evaluating the estimated model. However over fitted models have characteristics of high R-squared value and weak performance in predicting new data. Cross-validation was used to assure the accuracy and reliability of the fitted model and avoiding overfitting. In this method data were divided into two set. Training set were used for fitting the model that is used to predict the SARA score for the features in the test set. With cross-validation, addition to the value of explained variance by the fitted model (R-squared), the prediction accuracy of the fitted model were evaluated. This method was applied to assess the performance of the fitted model for the future sample data. (47).In this study cross-validation was implemented via Python 2011. Train_test_split function that split arrays or matrices into random train and test subsets were imported from the scikit-learn library to divide the data into training and test set. R-squared and A Residual sum of squares were reported to estimate the accuracy of the prediction.

Leave-one-out-cross-validation

In cross-validation data were divided into two sets and model were determined based on the training dataset and were examined for prediction of test data set. Significant Variability were observed for test data set. As dividing the data set, some of the data were removed from the dataset for test set and reliability of fitted model were decreased.

In this step for avoiding the loss of data and achieving more accuracy, another method for cross-validation was applied. Leave one out cross validation were used. In this approach, one of

the data were selected randomly for the testing set and rest of the data were used for estimation the model for each iteration. The fitted model was estimated by cross-validation over iterations.

Lasso regression

One of the best methods of linear regression to select and estimation of the model is the least absolute shrinkage and selection operator (LASSO).For less variability and more accurate prediction model performance, Lasso was applied due to the ability to select features automatically by shrinking the coefficients and equal them to zero. In this model the coefficients are estimated by the following formula; where β1, β2,…, β P are the coefficients.

$(\hat{\beta}0,\hat{\beta}lasso)=argmin\{\sum Ni=1(Yi-(\beta 0+\beta XTi))2+\lambda\sum Pj=1|||\beta j|||\}$

Y represents the Prediction of SARA score of the patients and X represents the features. λ is a positive characteristic of lasso regression that represents the quantity of shrinkage(regularization).the amount of shrinkage increase with the increase of the number of λ.Lasso solution path for λ was computed based on the coordinate_descent algorithm.(48)

lassoCV regression

For evaluating the best λ , RMSE and R-squared were examined. Different values of λ were tested to evaluate the minimum average error. Cross-validation applied to evaluate the expected error for each λ and selecting the optimized λ that minimizes the average error.LassoCV function from scikit-learn Linear-model package was used for fitting the model. This function is based on Least Angle Regression algorithm using cross-validation to estimate the best value of λ.(48)

Results

Linear regression

The data were analyzed by linear regression, using as predictors SARA score. The regression was a rather strong fit (R2= 84%), and the overall relationship was significant, F(3, 12) = 4.32, p = .04. With other variables held constant, scores were positively related to the features, increasing by 0.16 for every extra year of age, and by 0.09 for every extra pound per week income. Regression coefficients described in table 1. mean_absolute_error and mean_squared_error were estimated 0.44255522 and 0.32922330 in order.

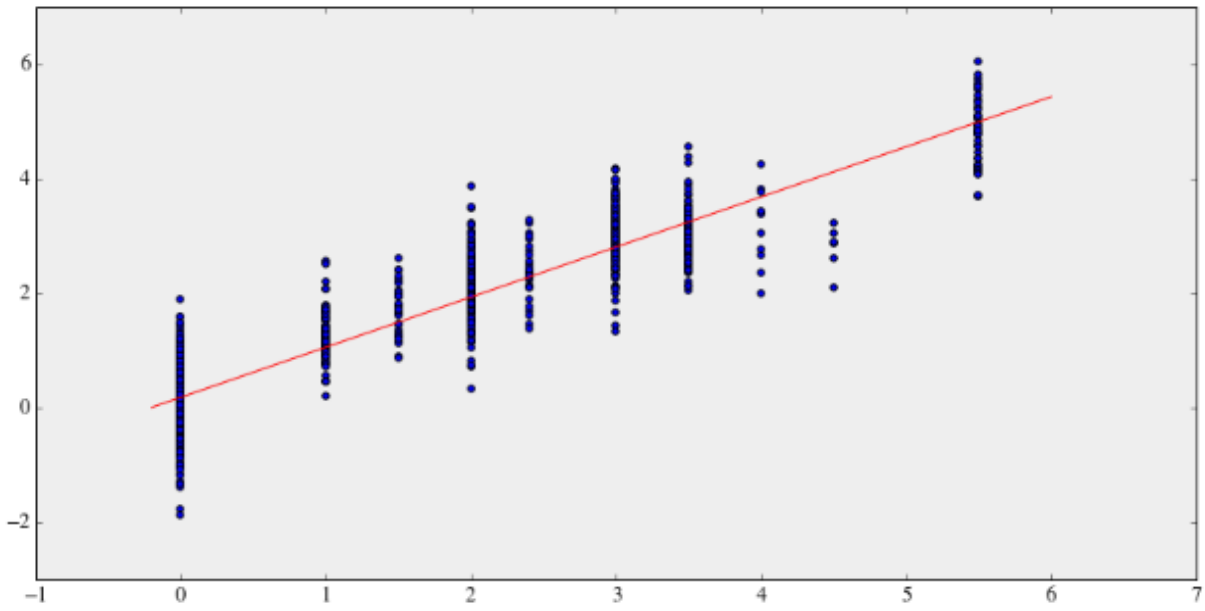

Figure: Fitted model result of Linear regression on features data and SARA score of patients. Score of patients vary from 0 with no ataxia to 7 most severe ataxia. linear model was rather a strong fit with R-squared =0.84%

count	120.000000
mean	0.000328
std	0.304404
min	-1.577632
25%	-0.004676
50%	-0.000052
75%	0.004425
max	1.760829

Table: This table shows the basic statistics of Coefficients for linear regression .

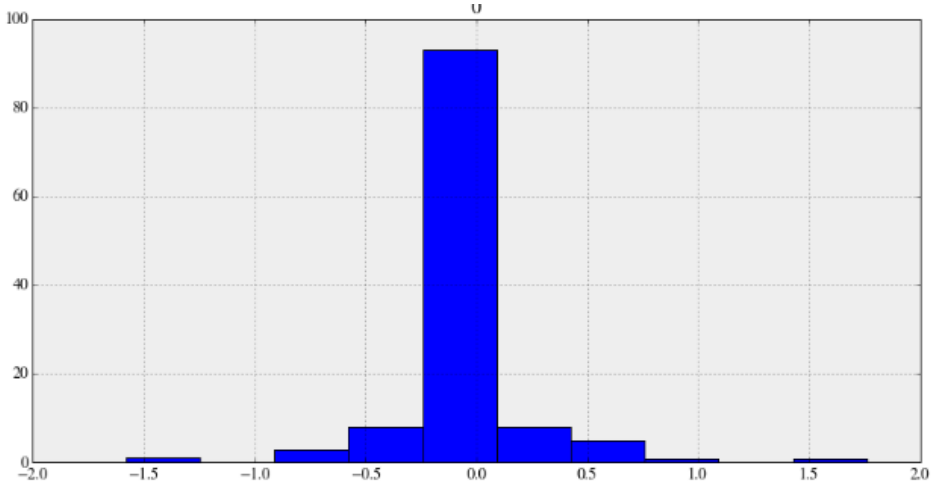

Figure: histogram of regression coefficients .This histogram illustrates that coefficients are small numbers and most of the coefficients are equals to zero.

Cross Validation

Cross-validation was applied for evaluation of accuracy of the regression model. Basic statistics of coefficients are shown in table. The results of the cross validation were satisfactory with explained variance score of (R2) 88% and the mean absolute error =0.41873424.The result of residual sum of squares equals to 0.20 and presents more accuracy and rather satisfactory model.

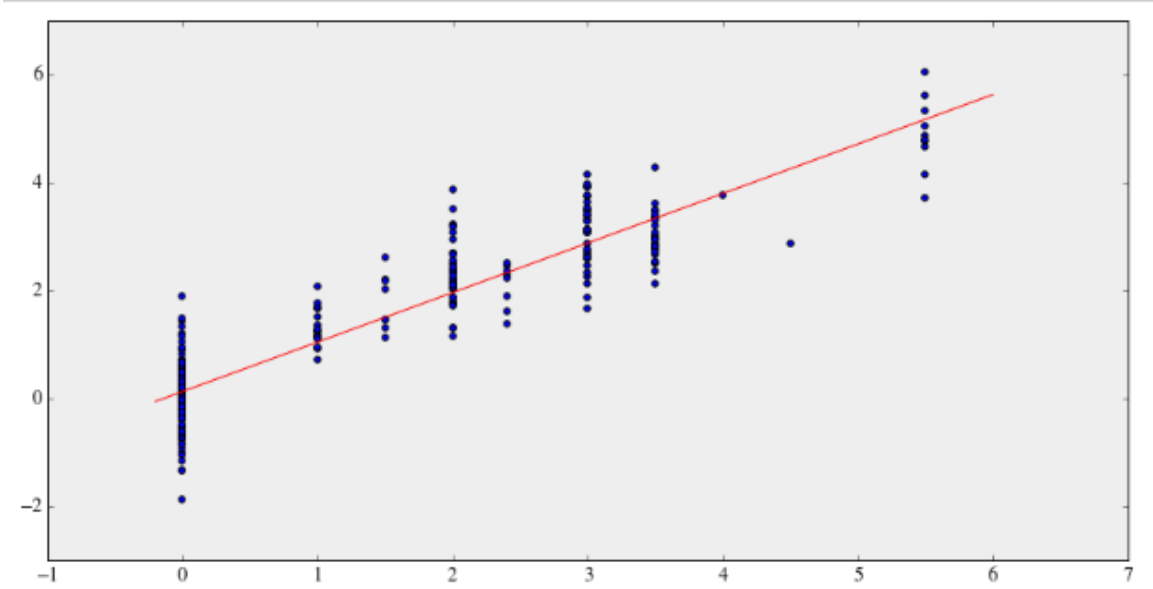

Figure: Fitted model result of Linear regression and cross validation on features data and SARA score of patients. Score of patients vary from 0 with no ataxia to 7 most severe ataxia. Prediction model was rather a strong fit with R-squared =0.88 and RSS=0.29 and mean absolute error=0.4

count	1.200000e+02
mean	4.389021e-03
std	2.677944e+11
min	-1.836912e+12
25%	-4.564800e-03
50%	2.405787e-04
75%	8.380951e-03
max	1.836912e+12

Table: This table shows the basic statistics of Coefficients for linear regression .

leave one out cross-validation

Another method of cross validation were applied for more accuracy due to removing one data for testing and modeling the fit base on the rest of the data. The result of leave one out cross validation were significantly good prediction with residual sum of squares of 0.33 , explained variance score(R2) of 0.85420914 and mean absolute error of 0.4.

Lasso Cross Validation regression:

The data were analyzed by lasso regression cross validation, using predictors SARA score. The regression was a rather strong fit (R2= 80%), and the overall relationship was significant, F(3, 12) = 4.32, p = .04. With other variables held constant, scores were positively related to the features. Basic descriptive statistics and regression coefficients are shown in Table 1.The result of lasso regression were evaluated by mean squared error of 0. 46 and the best lasso alpha of 0.16.

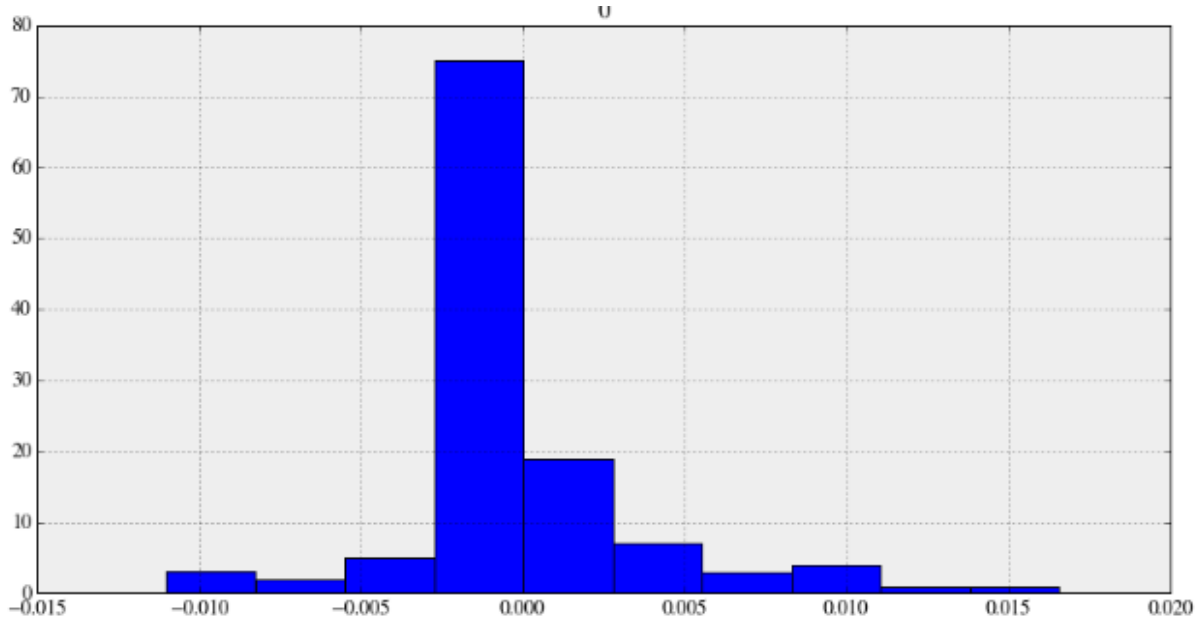

Figure: histogram of lassoCV regression coefficients .This histogram illustrates that coefficients are specifically so small numbers and most of the coefficients are equals to zero.

count	120.000000
mean	0.000363
std	0.003698
min	-0.010994
25%	-0.000048
50%	0.000000
75%	0.000784
max	0.016554

Table: This table shows the basic statistics of Coefficients for lassoCV regression .

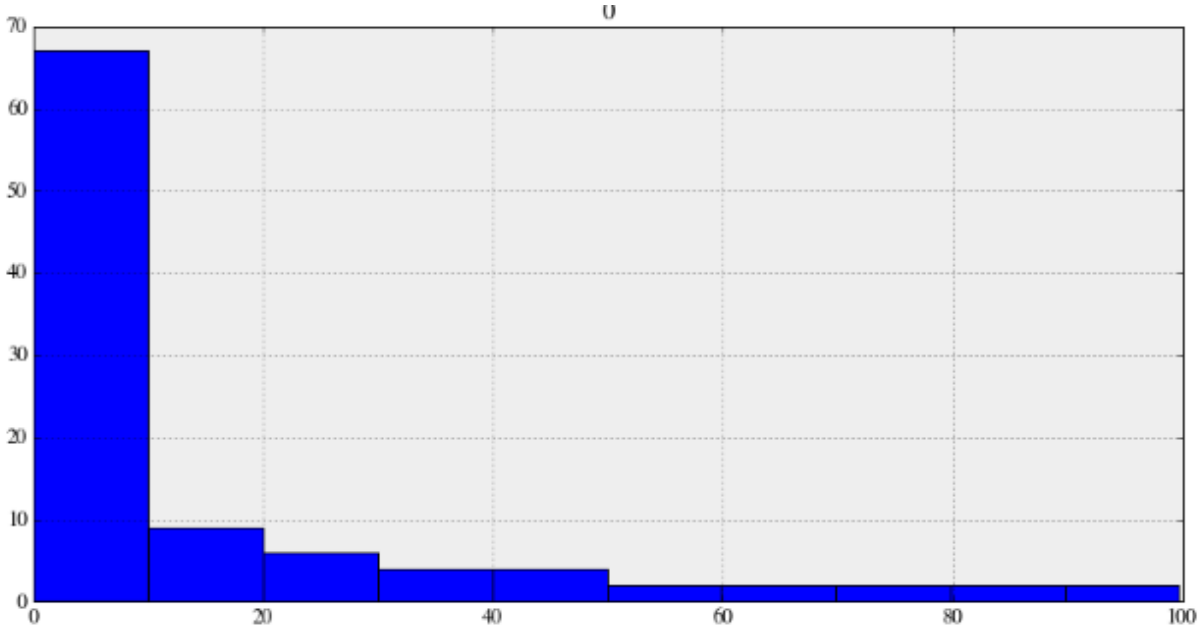

Figure: histogram of regularization parameter for lasso regression .

count	100.000000
mean	14.776893
std	23.453177
min	0.099684
25%	0.560819
50%	3.154212
75%	17.734837
max	99.684279

Table: This table shows the basic statistics of regularization parameter for lasso regression.

Referencing

1) Saute, J. A. M., Donis, K. C., Serrano-Munuera, C., Genis, D., Ramirez, L. T., Mazzetti, P., ... & Jardim, L. B. (2012). Ataxia rating scales—psychometric profiles, natural history and their application in clinical trials. *The Cerebellum*,*11*(2), 488-504

2) Morton, S.M. and Bastian, A.J., 2003. Relative contributions of balance and voluntary leg-coordination deficits to cerebellar gait ataxia. *Journal of neurophysiology*, *89*(4), pp.1844-1856.

3) Giles, L.L., DelBello, M.P., Gilbert, D.L., Stanford, K.E., Shear, P.K. and Strakowski, S.M., 2008. Cerebellar ataxia in youths at risk for bipolar disorder. *Bipolar disorders*, *10*(6), pp.733-737.

4) J, M., NK, C. & MT, B. " Brain Injury", *2004*,

5) Balliet, R., Harbst, K.B., Kim, D. and Stewart, R.V., 1986. Retraining of functional gait through the reduction of upper extremity weight-bearing in chronic cerebellar ataxia. *International rehabilitation medicine*, *8*(4), pp.148-153.

6) Kim, B.R., Lim, J.H., Lee, S.A., Park, S., Koh, S.E., Lee, I.S., Jung, H. and Lee, J., 2011. Usefulness of the Scale for the Assessment and Rating of Ataxia (SARA) in ataxic stroke patients. *Annals of rehabilitation medicine*,*35*(6), pp.772-780.

7) Saute, J.A.M., Donis, K.C., Serrano-Munuera, C., Genis, D., Ramirez, L.T., Mazzetti, P., Pérez, L.V., Latorre, P., Sequeiros, J., Matilla-Dueñas, A. and Jardim, L.B., 2012. Ataxia rating scales—psychometric profiles, natural history and their application in clinical trials. *The Cerebellum*, *11*(2), pp.488-504.

8) Pierce, S.B., Walsh, T., Chisholm, K.M., Lee, M.K., Thornton, A.M., Fiumara, A., Opitz, J.M., Levy-Lahad, E., Klevit, R.E. and King, M.C., 2010. Mutations in the DBP-deficiency protein HSD17B4 cause ovarian dysgenesis, hearing loss, and ataxia of Perrault Syndrome. *The American Journal of Human Genetics*, *87*(2), pp.282-288.

9) Cassidy, E., Kilbride, C., Holland, A. and Ataxia, U.K., 2009. Management of the Ataxias: towards best Clinical Practice.

10) Swift, M., Morrell, D., Massey, R.B. and Chase, C.L., 1991. Incidence of cancer in 161 families affected by ataxia–telangiectasia. *New England Journal of Medicine*, *325*(26), pp.1831-1836.

11) Wu, Y.R., Lin, H.Y., Chen, C.M., Gwinn-Hardy, K., Ro, L.S., Wang, Y.C., Li, S.H., Hwang, J.C., Fang, K., Hsieh-Li, H.M. and Li, M.L., 2004. Genetic testing in spinocerebellar ataxia in Taiwan: expansions of trinucleotide repeats in SCA8 and SCA17 are associated with typical Parkinson's disease. *Clinical genetics*, *65*(3), pp.209-214.

12) Schmitz-Hübsch, T., Du Montcel, S.T., Baliko, L., Berciano, J., Boesch, S., Depondt, C., Giunti, P., Globas, C., Infante, J., Kang, J.S. and Kremer, B., 2006. Scale for the assessment and rating of ataxia Development of a new clinical scale. *Neurology*, *66*(11), pp.1717-1720.

13) Azevedo, C.J., Walking With Ataxia.

14) Berglund, G., MOSSBERG, H.O. and Rydenstam, B., 1955. Acute cerebellar ataxia in children. *Acta paediatrica*, *44*(3), pp.254-262.

15) Schmitz-Hübsch, T., Du Montcel, S.T., Baliko, L., Berciano, J., Boesch, S., Depondt, C., Giunti, P., Globas, C., Infante, J., Kang, J.S. and Kremer, B., 2006. Scale for the assessment and rating of ataxia Development of a new clinical scale. *Neurology*, *66*(11), pp.1717-1720.

16) DSM-5 American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders. *Arlington: American Psychiatric Publishing*.

17) Bamford, J., Sandercock, P., Dennis, M., Warlow, C. and Burn, J., 1991. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *The Lancet*, *337*(8756), pp.1521-1526.

18) Storey, E., Tuck, K., Hester, R., Hughes, A. and Churchyard, A., 2004. Inter-rater reliability of the International Cooperative Ataxia Rating Scale (ICARS).*Movement disorders*, *19*(2), pp.190-192.

19) Braga-Neto, P., Godeiro-Junior, C., Dutra, L.A., Pedroso, J.L. and Barsottini, O.G.P., 2010. Translation and validation into Brazilian version of the Scale of the Assessment and Rating of Ataxia (SARA). *Arquivos de neuro-psiquiatria*,*68*(2), pp.228-230.

20) Lawerman, T.F., Brandsma, R., Geffen, J.T., Lunsing, R.J., Burger, H., Tijssen, M.A., Vries, J.J., Koning, T.J. and Sival, D.A., 2016. Reliability of phenotypic early-onset ataxia assessment: a pilot study. *Developmental Medicine & Child Neurology*, *58*(1), pp.70-76.

21) Martinez-Manzanera O, Lawerman TF, Blok HJ, Sival DA and Maurits NM "Analysis of the finger-to-nose test in patients with ataxia, patients with developmental coordination disorder and controls" in preparation

22) Globas, C., du Montcel, S.T., Baliko, L., Boesch, S., Depondt, C., DiDonato, S., Durr, A., Filla, A., Klockgether, T., Mariotti, C. and Melegh, B., 2008. Early symptoms in spinocerebellar ataxia type 1, 2, 3, and 6. *Movement disorders*, *23*(15), pp.2232-2238.

23) Hadjivassiliou, M., Mäki, M., Sanders, D.S., Williamson, C.A., Grünewald, R.A., Woodroofe, N.M. and Korponay-Szabó, I.R., 2006. Autoantibody targeting of brain and intestinal transglutaminase in gluten ataxia. *Neurology*,*66*(3), pp.373-377.

24) Manto, M., Bower, J.M., Conforto, A.B., Delgado-García, J.M., da Guarda, S.N.F., Gerwig, M., Habas, C., Hagura, N., Ivry, R.B., Mariën, P. and Molinari, M., 2012. Consensus paper: roles of the cerebellum in motor control—the diversity of ideas on cerebellar involvement in movement. *The Cerebellum*, *11*(2), pp.457-487.

25) Schmahmann, J.D., 2004. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *The Journal of neuropsychiatry and clinical neurosciences*.

26) Adler, C.H. and Ahlskog, J.E. eds., 2000. *Parkinson's disease and movement disorders: diagnosis and treatment guidelines for the practicing physician*. Springer Science & Business Media.

27) Schöls, L., Bauer, P., Schmidt, T., Schulte, T. and Riess, O., 2004. Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. *The Lancet Neurology*, *3*(5), pp.291-304.

28) Armutlu, K., 2013. Ataxia: Physical therapy and rehabilitation applications for ataxic patients. *International encyclopedia of rehabilitation. http://cirrie. buffalo. edu/encyclopedia/en/article*.

29) Lenneberg, E.H., Chomsky, N. and Marx, O., 1967. *Biological foundations of language* (Vol. 68). New York: Wiley.

30) Jürgens, U., 2002. Neural pathways underlying vocal control. *Neuroscience & Biobehavioral Reviews*, *26*(2), pp.235-258.

31) Berardelli, A., Hallett, M., Rothwell, J.C., Agostino, R., Manfredi, M., Thompson, P.D. and Marsden, C.D., 1996. Single–joint rapid arm movements in normal subjects and in patients with motor disorders. *Brain*,*119*(2), pp.661-674.

32) Goodkin, H.P., 1993. Preserved simple and impaired compound movement after infarction in the territory of the superior cerebellar artery. *Canadian Journal of Neurological Sciences/Journal Canadien des Sciences Neurologiques*, *20*(S3), pp.S93-S104.

33) Bareš, M., Lungu, O.V., Husárová, I. and Gescheidt, T., 2010. Predictive motor timing performance dissociates between early diseases of the cerebellum and Parkinson's disease. *The Cerebellum*, *9*(1), pp.124-135.

34) GILMAN, S., 1969. THE MECHANISM OF CEREBELLAR HYPOTONIA1.*Brain*, *92*, pp.621-638.

35) Gilman, S., 1981. BLOEDEL JR, AND LECHTENBERG R. *Disorders of the Cerebellum*.

36) Topka, H., Konczak, J., Schneider, K., Boose, A. and Dichgans, J., 1998. Multijoint arm movements in cerebellar ataxia: abnormal control of movement dynamics. *Experimental brain research*, *119*(4), pp.493-503.

37) Winter, D.A., 2009. *Biomechanics and motor control of human movement*. John Wiley & Sons.

38) Stolze, H., et al. "Typical features of cerebellar ataxic gait." *Journal of Neurology, Neurosurgery & Psychiatry* 73.3 (2002): 310-312.

39) Saute, J.A.M., Donis, K.C., Serrano-Munuera, C., Genis, D., Ramirez, L.T., Mazzetti, P., Pérez, L.V., Latorre, P., Sequeiros, J., Matilla-Dueñas, A. and Jardim, L.B., 2012. Ataxia rating scales—psychometric profiles, natural history and their application in clinical trials. *The Cerebellum*, *11*(2), pp.488-504.

40) Matsushima, A., Yoshida, K., Genno, H., Murata, A., Matsuzawa, S., Nakamura, K., Nakamura, A. and Ikeda, S.I., 2015. Clinical assessment of standing and gait in ataxic patients using a triaxial accelerometer.*Cerebellum & ataxias*, *2*(1), p.1.

41) Notermans, N.C., Van Dijk, G.W., Van der Graaf, Y., Van Gijn, J. and Wokke, J.H., 1994. Measuring ataxia: quantification based on the standard neurological examination. *Journal of Neurology, Neurosurgery & Psychiatry*,*57*(1), pp.22-26.

42) Matsushima, A., Yoshida, K., Genno, H., Murata, A., Matsuzawa, S., Nakamura, K., Nakamura, A. and Ikeda, S.I., 2015. Clinical assessment of standing and gait in ataxic patients using a triaxial accelerometer.*Cerebellum & ataxias*, *2*(1), p.1.

43) Zijlstra, W. and Hof, A.L., 2003. Assessment of spatio-temporal gait parameters from trunk accelerations during human walking. *Gait & posture*,*18*(2), pp.1-10.

44) Sejdic, E., Lowry, K.A., Bellanca, J., Perera, S., Redfern, M.S. and Brach, J.S., 2016. Extraction of Stride Events From Gait Accelerometry During Treadmill Walking. *Translational Engineering in Health and Medicine, IEEE Journal of*, *4*, pp.1-11.Kutner, M.H., 1996. *Applied linear statistical models* (Vol. 4, p. 318). Chicago: Irwin.

45) Seber, G.A. and Lee, A.J., 2012. *Linear regression analysis* (Vol. 936). John Wiley & Sons.

46) Shao, J., 1993. Linear model selection by cross-validation. *Journal of the American statistical Association*, *88*(422), pp.486-494.

47) Tibshirani, R., 1996. Regression shrinkage and selection via the lasso.*Journal of the Royal Statistical Society. Series B (Methodological)*, pp.267-288.

Appendix