Eye Movement Measures in Schizophrenia

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by

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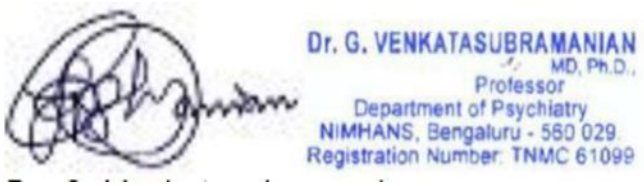
CERTIFICATE

This is to certify that this dissertation entitled "**Eye Movement Measures in Schizophrenia**" towards the partial fulfilment of the BS-MS dual degree programme at the Indian Institute of Science Education and Research, Pune represents study/work carried out by Raghuram H V at National Institute of Mental Health and Neuro Sciences (NIMHANS) under the supervision of Dr G. Venkatasubramanian, Professor, NIMHANS during the academic year 2018-19.



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DECLARATION

I hereby declare that the matter embodied in the report entitled "**Eye Movement Measures in Schizophrenia**" are the results of the work carried out by me at the Department of Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), under the supervision of Dr G. Venkatasubramanian and the same has not been submitted elsewhere for any other degree.

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ABSTRACT

Among the contemporary techniques used to study the human brain, eye tracking is one of the most effective tools to study attention and decision making. By providing information about the gaze position, gaze direction, eye movements (saccades, fixations, etc) and pupil size, eye tracking has several applications not only in psychology but also in psychiatry, gaming, advertising, etc. Since eye movement abnormalities had been identified in various psychiatric disorders, studying eye movements using eye tracking provides one an economical, accessible and accurate tool to detect and diagnose these disorders.

In this project, we focussed mainly on developing a novel methodology to analyse EyeLink eye tracking data using PyGaze, an open-source Python toolbox. The methodology was then used to analyse the eye movement data from healthy controls and patients with Schizophrenia. Measures for the eye movement paradigms were extracted using the developed methodology.

A very high degree of reliability was found between the results from the EyeLink data viewer and the developed methodology for the antisaccade paradigm measures. Most of the fixation stability test measures were found to be statistically significant when compared across healthy controls and schizophrenic patients, and the results obtained were consistent with other studies. The measures, extracted using the developed methodology, could be developed into potential behavioral biomarkers to aid in the research on psychiatric disorders like Schizophrenia.

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CHAPTER 1

INTRODUCTION TO EYE TRACKING

Only a generation ago, eye tracking required very expensive and sophisticated instruments and also, the researcher was required to be specialized in eye tracking (technical as well as experimental). Due to this, acquisition and analysis of eye movement data were often slow and arduous. Therefore, it is normal to expect that eye tracking appealed to very few researchers. However, due to the recent and rapid development in both the eye tracking software and hardware (like the increased computer processor speed and improved computer vision approaches), new devices are being developed which are significantly better in their usability, speed, accuracy, and cost (Duchowski, 2007). It is now becoming more of a tool and less of a novelty.

Eye tracking is a technique generally used to measure eye movements. It measures the position of the eyes (relative to the head position). One of its main advantages is its property of automatic detection, which increases accuracy and reduces variability. Eye trackers (Figure 1) are generally used to record eye positions and their movements. In addition to recording the gaze position, they provide other useful information regarding pupil size (area or diameter), blink rate, etc. Regular eye movement mainly consists of fixations and saccades (except during smooth pursuits and blinks). The sampling frequency, which limits the number of data points recorded by the eye tracker, is the number of times an eye position is recorded in one second. If one uses an eye tracker having high sampling frequency, one will be able to predict the eye movement at a higher accuracy.

Figure 1: EyeLink 1000 (SR Research, Canada)

Although eye tracking presents an objective view of human visual and attentional processes, it hasn't yet been used widely other than for research purposes. Eye tracking has applications not only in psychology and neuroscience but also in psychiatry, vehicle simulations (car, aeroplane, etc), gaming, marketing, advertising, human-computer interactions (HCI), virtual reality, web design, learning and education, etc (Duchowski, 2007). Here, we'll mainly be focussing on the role of eye tracking in psychiatry (and neurological disorders). Although data from other modalities like brain imaging, electroencephalography (EEG), molecular and genetic studies are mainly used for the detection and diagnosis of psychiatric disorders, eye tracking is one of the least explored techniques which can be used to assess the disorders. Although eye tracking isn't much explored, it's very much open to design and experimentation and with the recent development of relatively cheap eye trackers, it reduces the cost of conducting research.

1.1 Eye tracking in Psychiatry:

A psychiatric or mental disorder, according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders), is a psychological or behavioral syndrome characterized by either disability or emotional distress or an increased risk of pain or disability or even death (Stein et al., 2010). Depression, schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), etc are some of the major psychiatric disorders. It is currently estimated that every 1 in 6 people in the world (i.e. approximately 1 billion of the world's population) are suffering from one or more mental disorders (Ritchie and Roser, 2018). According to the National Mental Health Survey of India, 2015-16 conducted by NIMHANS, approximately 10% of the Indian population are affected by common mental disorders like depression whereas approximately 0.8% of the population is affected by severe mental disorders like schizophrenia, bipolar disorder, etc (Gururaj et al., 2016). Also, nearly 150 million Indians are in dire need of active treatment for the disorders (Gururaj et al., 2016). Psychiatric disorders are among the most burdensome of all disorders since they are widespread, chronic, have an early age of onset, and cause disability ("Cross-national comparisons", 2000). Although various studies point to the growing burden of mental disorders, their extent and their pattern are not clearly known. Though unmeasured, the ramifications on the socio-economic conditions are huge.

Understanding eye movements and their abnormalities will be very useful in psychiatry as they will not only help us to elucidate the pathophysiology and the neurobiological correlates of psychiatric disorders but may also aid in their detection and diagnosis. Most commonly studied eye movements are saccades and smooth pursuits. Diefendorf and Dodge in 1908, were one of the first to study eye movements in a clinical population who reported abnormalities in eye movement patterns in patients with mental illness. They also reported variation in smooth pursuit movement in patients with schizophrenia when compared to healthy persons (Diefendorf and Dodge, 1908). Despite their work, few groups worked on eye movement data from psychiatric patients until the 1970s. In 1973, Holzman adopted Diefendorf and Dodge's approach to study smooth pursuit eye movements in patients with Schizophrenia which showed that smooth pursuit movements were impaired in schizophrenic patients (Holzman et al., 1973). This seminal study led to active oculomotor research in psychiatry.

Table 1 shows the eye movement abnormalities present in different psychiatric disorders.

Mental Disorder	Eye movement abnormalities	Study
Schizophrenia	Impaired smooth pursuit (reduced smooth pursuit gain); Increased error rates in the antisaccade task	Hutton et al., 1998; Levy et al., 1993; O'Driscoll and Callahan, 2008
Bipolar Disorder	Increased errors in the antisaccade task	Carvalho et al., 2015; Tien et al., 1996
Depression	Longer latency and error rates in antisaccade task; shorter fixation duration and larger saccade amplitudes in fixation task	Li et al., 2016
OCD	Smooth pursuit dysfunction	Sweeney et al., 1992
ADHD	Higher rates of blinks and microsaccades	Fried et al., 2014
Autism Spectrum Disorder	Reduced accuracy, reduced saccade peak velocity in a visually guided saccade task; smooth pursuit deficits	Schmitt et al., 2014; Takarae, 2004

Table 1: Eye movement abnormalities in various psychiatric disorders

There are various attributes of eye movements which makes them very useful to study psychiatric disorders (Klein and Ettinger, 2008; Liversedge et al., 2011):

1. The neural mechanisms of eye movements (and the neuroanatomy) are well understood from single unit recordings, lesions and imaging studies.
2. Eye movements are relatively inaccessible to arbitrary modification or simulation.
3. The tasks are simple to understand and the responses required are fairly easy.
4. The eye movements can be measured by various reliable techniques, which also provide information about the eye position over time which allows for quantification of eye movement measures.

Schizophrenia is a chronic neuropsychiatric disorder which is known to be extremely debilitating in nature. It affects people across all cultures and socio-economic groups. Schizophrenia is placed among the top ten leading causes of disability in the world. It is the most expensive of all the mental disorders (Kurtz, 2016). It affects approximately 0.3-0.5% of the global population and its prevalence in India is around 0.25% (Ritchie and Roser, 2018).

Various eye movement abnormalities have been extensively studied in patients with Schizophrenia. Reduced smooth pursuit velocity gain (in smooth pursuit task), increased antisaccade error rates (in antisaccade task) and other abnormalities have been consistently observed in schizophrenic patients (Hutton et al., 1998; Levy et al., 1993; O'Driscoll and Callahan, 2008). Studying eye movements provides one an economical, accessible and accurate technique not only to understand the neural basis of the disorder but also aid in the diagnosis and treatment in Schizophrenia.

1.2 Review of Literature:

The highest density of cones is known to be present in the fovea centralis, located in a small region of the retina. Due to this, the fovea has the highest spatial resolution in the retina. So, in order to focus an object of interest, it is necessary for the eye to move in order to maintain the object on the fovea. Therefore, eye movements are necessary for visual perception. They can be mainly classified into the following types - saccades, fixations, smooth pursuit eye movements, vestibulo-ocular reflex and vergence movements (Purves et al., 2001).

Fixation is the maintenance of the visual gaze on a particular location. Fixations stabilize the retina over an object of interest. During fixation, the eyes are relatively stationary and the object of interest is on the fovea. Therefore, most of the visual processing occurs during fixations. Eye movements (like microsaccades, ocular drifts, and ocular microtremors) occur even during fixations (Rucci and Poletti, 2015; Rucci et al., 2016).

Saccades are rapid, ballistic eye movements which serve to foveate a target or an object of interest by changing the point of fixation. They generally occur between two phases of fixation. They are termed to be ballistic because changes in target position during the course of eye movement cannot be responded until the saccade is completed. The time required to initiate a saccade (i.e. latency) is around 200ms. The saccadic eye movements last for 15-100ms depending upon their amplitude (Purves et al., 2001). They can either be reflexive (E.g. scanning saccade generated to explore the surroundings) or voluntarily generated (E.g. antisaccade). Prosaccade is a saccade made towards a sudden onset target. Antisaccade is a volitional saccade made at the mirror image location of the onset target. This requires higher cognitive processes such as inhibition (i.e. suppressing the reflexive response of looking at the onset target) and spatial memory, which helps in the generation of an endogenous saccade to the mirror image location of the target (Liversedge et al., 2011).

Saccade parameters (Holmqvist et al., 2011):

- Amplitude (measured in degrees) is the distance travelled from the onset to the offset of a saccade.
- Amplitude gain is the ratio of actual saccade amplitude to that of the target amplitude.
- Peak velocity (measured in degree/sec) is the maximum velocity reached during a saccadic eye movement.
- Latency (measured in ms) is a measure of the difference in time from the onset of a target until the onset/beginning of the first saccade.
- Scanpath is a sequence of all events (fixations or saccades) in space within a time period.
- Scanpath length (measured in degrees) is the sum of all saccadic amplitudes present in the scanpath.

Smooth pursuit eye movements are slow, controlled eye movements which help to maintain a moving target on the fovea. They are generally involved when tracking a moving target and are under voluntary control. These movements can match the velocity of the moving target (if its velocity < 30m/s). A catch-up saccade is first generated, when the target starts moving, in order to foveate the target. After this, the eye tracks the target smoothly (Purves et al., 2001).

Vestibulo-ocular eye movements compensate for any head movement by stabilising the eyes relative to the object of interest/scene. These movements prevent the target or object from "slipping" from the fovea as the head moves. Activation of the vestibular apparatus due to head rotation generates an excitatory signal to the extraocular muscles on one side and an inhibitory signal to the muscles on the other side (Purves et al., 2001).

Vergence movements are disconjugate (i.e. both eyes move in the opposite direction) eye movements which involve either convergence or divergence of each eye in order to see a target that is either close or far away from the observer (Purves et al., 2001).

Techniques to record eye movements -

The eye tracker is the most commonly used device to measure eye position and record its movements. The eye tracking techniques are categorised either as the one that measures the eye position relative to the head or the one that measures the orientation of eye in space i.e. the point of regard. Video-based eye trackers typically measure the point of regard (Duchowski, 2007). The different techniques are described below:

1. Electro-OculoGraphy (EOG) relies on measuring the electric potential differences of the skin using the electrodes placed around the eye. The electrode pairs are placed either right and left or above and below the eyes. These electrodes create a steady electric potential between the retina and the cornea. Any eye movement leads to a change in the electric potential. This measures eye positions relative to the head and therefore is not suitable for any point of regard measurements. Although this technique has disadvantages like poor gaze direction accuracy, it is still used today (since it's cheap and non-invasive) (Duchowski, 2007; Holmqvist et al., 2011).

2. Scleral contact lens/Search coils technique involves a wire coil fixed or embedded onto a contact lens which is then worn on the eye. Mechanical or optical reference objects are attached to the lens. When the coil moves in an electromagnetic field, it induces a voltage in the coil. It has a very high spatial and temporal resolution due to which it can even detect very small eye movements accurately. But since this technique requires insertion of the lens on the eyes (invasive in nature), it is rarely used. This technique also measures the eye position relative to the head (Duchowski, 2007; Holmqvist et al., 2011).

3. Video-OculoGraphy (VOG) involves a wide range of recording techniques which includes measuring eye features in motion or under rotation. These features generally include the shape of the pupil, the location of the iris-sclera boundary, corneal reflections (or purkinje images) due to a nearby light source, etc. These techniques also don't provide 'point of regard' measurements. The eye movements are typically recorded manually on a videotape which can be laborious and error-prone. Also, this technique is limited by the sampling rate of the recording device (Duchowski, 2007).

4. Optical tracking or Video-based corneal reflection technique provides the point of regard measurements. The head position should be fixed (using headrest or chinrest) so that the eye position (relative to the head) is measured or multiple points of reference (i.e. different eye features) must be considered to distinguish eye movements from the head movements. Corneal reflection (due to the infra-red light source) and location of the pupil center are two such features that are considered. The underlying principle behind this technique is Pupil Center Corneal Reflection (PCCR). Video-based corneal reflection eye trackers use relatively inexpensive, high-resolution cameras along with infra-red light source and image processing hardware to compute eye movements (i.e. point of regard). Head movements are restrained using head/chin rest. They are widely used for eye tracking since they are non-invasive and inexpensive. They are more suitable for interactive systems (Duchowski, 2007; Holmqvist et al., 2011).

Principle behind the working of video-based eye trackers -

Video-based eye trackers contain an illuminator (infra-red light source) and a camera (Figure 2) which takes a sequence of images. The number of images captured by the camera (in the eye tracker) depends upon the sampling frequency of

the eye tracker (in case of EyeLink 1000, 1000 Hz is the sampling frequency and 1000 images taken every second). For each image, the pupil center and the corneal reflection is identified with the help of image processing algorithms (present in the eye tracker software). Corneal reflection (the reflection of the infrared illuminator present next to the camera) used by the eye trackers is actually the first Purkinje image of the eye (Figure 2).

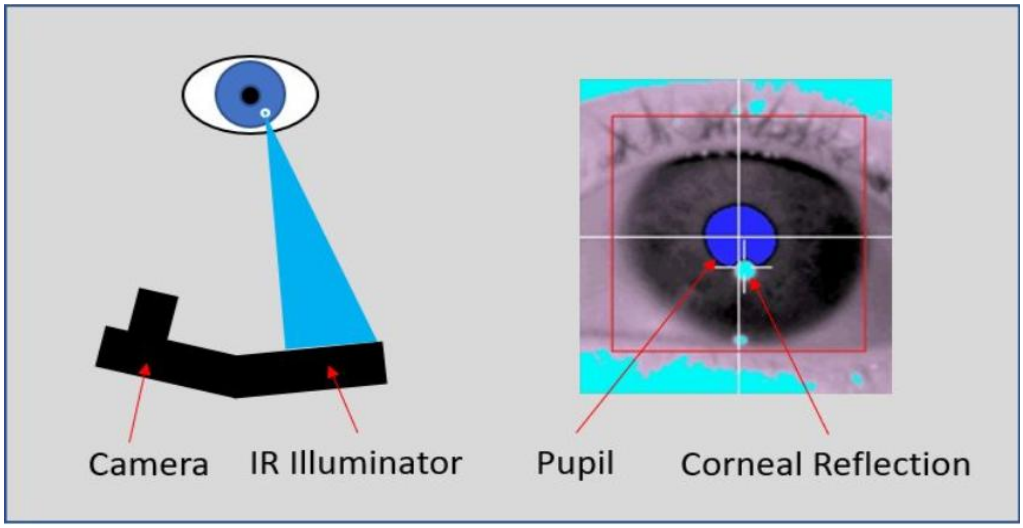


Figure 2: Pupil Center Corneal Reflection (from S. Hutton, 2018)

The center of the corneal reflection is commonly calculated relative to the pupil center. When the eye rotates, the pupil center changes its position, but the corneal reflection (considering that the head movements are restrained) remains relatively fixed. This is because the light source (i.e. infra-red illuminator) is fixed relative to the camera. Therefore during eye rotation the pupil center moves whereas the center of corneal reflection remains fixed.

However, if small head movements occur despite restraining the head using head/chin rest, the eyes remain relatively fixed but the positions of both the pupil center and the corneal reflection center are shifted. Therefore, the relationship or the positional difference between the pupil center and the center of corneal reflection remains constant during head movements whereas during rotation, it changes. The present video-based eye trackers capitalize on this difference in the relationship between the pupil center and corneal reflection to compensate for any shifts in head position. The Euclidean vector between the pupil center and the center of corneal reflection is generally used to measure gaze direction. It can also help to determine whether the difference (pupil center position - corneal reflection center position) is a

result of actual eye rotation or a result of a change in head position (Duchowski, 2007; Holmqvist et al., 2011; S. Hutton, 2018).

Table 2 provides a list of possible open-source toolboxes/software which could be used to analyse eye tracking data.

Toolbox/Software (reference)	Programming Language (if required)	Features	Reasons for not choosing the toolbox/software for data analysis
PyGaze (Dalmaijer et al., 2014)	Python	Compatible with EyeLink, gaze visualizations	-
Eyelinker	R	Reads EyeLink ASC files; Identify and label events in raw data	No tools available for visualization or analysis
Eyetracking R (Dink and Ferguson, 2015)	R	Different type of data analyses available; supports EyeLink	Mainly suitable for Area of Interest calculation
ETRAN (Zhegallo and Marmalyuk, 2015)	R	Gaze data Visualizations	Doesn't support data from Eyelink eye tracker
Gazealyze (Berger et al., 2012)	MATLAB	Batch processing, Gaze visualizations	MATLAB license needs to be purchased (not open-source)
EyeTrace (Kübler et al., in press)	-	Gaze, saccade and fixation visualization and statistics	Unavailability of plugin for EyeLink eye tracker

Table 2: List of possible open-source toolbox/software to analyse eye tracking data

Several studies have shown that eye movement abnormalities are potential behavioral as well as neurophysiological biomarkers for Schizophrenia which can be used both as a tool to aid in the diagnosis of Schizophrenia and to discriminate Schizophrenic patients from healthy controls (Benson et al., 2012; Miura et al., 2014; Morita et al., 2017). Various measures were collected from different eye movement paradigms. The metrics/measures for fixation stability test were chosen from these studies. These include number of fixations, fixation duration, number of saccades, saccade amplitude and scanpath length. The measures, which were shown to be

statistically significant when compared across controls and patients, were used to build classifier models (Benson et al., 2012).

Fixation stability has commonly been quantified using BCEA. BCEA, which refers to bivariate contour ellipse area, is an indirect measure of fixation stability. It is defined as calculating the area of an ellipse which encloses all fixation data points for a given proportion of eye positions during a fixation trial (Steinman,1965). It is generally used to quantify fixation stability. Generally, smaller values of BCEA correlate to more stable fixation whereas higher values correlate to poorer fixation stability (Crossland and Rubin, 2002; Crossland et al., 2004).

The performance measures for the antisaccade paradigm were chosen from Subramaniam et al. (2018) where they had calculated these measures using the EyeLink data viewer and Excel Macros.

1.3 Limitations and Factors influencing eye tracking data:

Although eye tracking assists in measuring and quantifying eye movements, it has a few limitations (Bryn Farnsworth, 2019).

- It isn't suitable for studying peripheral vision.
- While it can inform what the subjects are looking at, it can't reveal their thoughts or what they perceive.

Factors which affect eye tracking data quality are as follows (Holmqvist et al., 2012):

- Different eye physiologies of the test subjects (or participants) and their ability to follow the given instructions. Some of them may wear glasses or contact lens, or have long eyelashes which may hinder the image taken and hence the data quality.
- Operators who conduct the experiments have varying skills (like adjusting the camera, recalibration, providing instructions, etc) and experience in recording the data.
- The task can also affect data quality. If the task induces the subject to blink more often, it leads to loss of data (not applicable if blink events are considered for analysis).
- The environment in which the experiment was recorded (like controlled laboratory settings or outdoors, presence of any vibrations, etc) should also be considered as they can strongly influence the data quality.

1.4 Need for the study:

EyeLink 1000 eye tracker (SR Research, Canada) (Figure 1) has a sampling frequency of 1000 Hz and it has the ability to record data from the eyes (i.e. binocular). It records the subject's eye movements and stores them in the EyeLink data file (EDF) format. EyeLink data viewer application is generally used to read and extract data from the EDF files. It is also used for viewing, filtering and analyzing gaze data. The data viewer can either generate reports (.xls or .txt format) based on saccades, fixations, etc or on individual trials. These reports can be imported directly into Excel or statistical packages like SPSS or R for further statistical analysis.

However, EyeLink data viewer requires a license key which needs to be purchased and is very expensive. Without the license key, it's not possible to use the EyeLink data viewer for reading the eye movement data. The data viewer is only able to read data from EyeLink eye-tracker, and not from other eye-tracker brands. Also, the data cannot be completely analyzed in the EyeLink data viewer. The data has to be taken out and analysed using other tools (like Excel, R, etc).

If one uses an open-source toolbox/software to analyse the eye tracking data, this provides user flexibility and the ease of handling everything on a single platform. Sharing and converting data to different formats (like .csv, .txt, .xlsx, etx) becomes very easy if one doesn't rely on EyeLink data viewer. Using an open-source toolbox/software, one can easily represent the results in multiple ways (either in the form of tables, graphs, images, etc). Therefore, a new methodology needs to be developed with the help of an open-source toolbox/software to read and analyse EyeLink eye tracking data without using the EyeLink data viewer.

1.5 Objectives:

The main objective of the project was to develop a methodology to analyse eye movement data recorded using EyeLink eye tracker with the help of an open-source toolbox/software. We would then test the new methodology by analysing eye movement data collected from healthy controls and patients with Schizophrenia. The other objectives were to find and extract the measures for the fixation stability test and calculate these measures for both the healthy controls and the schizophrenic patients. Also, it was attempted to reproduce the measures for antisaccade paradigm using the developed methodology.

CHAPTER 2

METHODOLOGY

Here, we'll mainly discuss regarding the selection of the open-source toolbox or software required for post-acquisition analysis of eye tracking data (mainly from EyeLink eye trackers). We'll then explain how the pipeline for eye tracking analysis was developed. Then we'll touch upon the eye movement recordings, paradigms, data processing, and data analysis.

2.1 Selection of the open-source toolbox/software:

The data viewer can read data only from a specific eye tracker, its license key is very expensive and it doesn't allow sharing across groups. Also, it doesn't provide flexibility to the user and the data needs to be handled across multiple platforms. Therefore, it is essential to develop a methodology to analyze EyeLink eye tracking data without using the data viewer. If possible, the new methodology should be able to read data from multiple eye tracker brands. Open-source packages, toolboxes or software, compatible with any open-source programming language like Python, R, etc can be used for the analysis of eye movement data. Some of these toolboxes along with their source code are easily accessible, which can be modified according to one's requirements.

Criteria for selecting such toolbox, package or software:

- Visualization of eye movement data in the form of raw traces and attention maps (like heatmaps and fixation maps).
- Replicating the results produced by the EyeLink data viewer i.e. calculating the metrics that are already present in the software.
- Identifying and calculating new metrics that are not included in the software.

These measures could be developed into a potential behavioral biomarker (in addition to the clinical measures) to predict the onset or to identify persons at increased risk of developing Schizophrenia.

PyGaze was selected from Table 2 to be used for developing a pipeline for analysis of eye tracking data. PyGaze is an open-source, cross-platform Python toolbox designed mainly for eye tracking experiments. It is user-friendly in terms of programming ease and script readability without compromising functionality and

flexibility. It supports multiple operating systems (Windows, Linux, and Mac OSX) and is compatible with multiple eye tracker brands (SR Research's EyeLink, SMI and Tobii systems). PyGaze also supports data acquisition from various eye trackers. Everything from stimulus presentation to eye-tracker communication and analysis can be handled via PyGaze scripting. Also, the same Python script (with a little modification) can be used with data from different eye trackers. The source code for PyGaze is easily accessible which can be freely used and modified, not only by researchers but by other companies interested in eye tracking as well (Dalmaijer et al., 2014). Also, Python has extensive libraries and packages and supports batch processing of data files (i.e. running all files with minimum user interaction).

2.2 Development of the pipeline for eye movement data analysis:

EyeLink data file (EDF) format is a platform-portable highly compressed binary format which is either directly used by EyeLink Data Viewer software or converted by EDF2ASC utility into a more readable text format. It consists of time synchronized eye position samples(ms) and events (can be either fixations, saccades, etc), generally organized in the form of blocks. Pupil size can also be recorded. Since the EDF file is present in a compressed binary format, it's hard to access the data. To make the data more accessible, EDF2ASC utility translates the file into a text format which is easily accessible and easier to work with. The ASC file contains lines of text, with each line representing data for a single sample, event or other parameters (file description, comments, etc). The ASC file is divided into blocks indicated by START and END events ("SR RESEARCH", 2007; "SR RESEARCH", 2014).

The data files from the eye trackers consist of samples (eye position and pupil diameter) and events (information that indicates something has occurred like start/end of fixation, saccade, etc). Each sample is associated with a timestamp (measured from the time when the tracker software was started).

EyeLink developer's kit is a tool developed to convert the EyeLink EDF file to ASC file. It consists of an EDF2ASC translator which mainly converts the samples and events present in the EDF file into lines of text. The output data from the EDF file can either contain samples, events or both depending on the user's preference ("SR RESEARCH", 2007; "SR RESEARCH", 2014).

PyGaze is an open-source Python package mainly used for performing eye-tracking experiments and analysis. PyGaze Analyser library is required to read EyeLink ASC files. It contains functions to read and extract data from EyeLink, EyeTribe, SMI and other eye trackers. It also provides visualization functions for plotting gaze data. The *read_edf* function in PyGaze analyser reads EyeLink ASC files and takes these arguments: name/path of the data file, an event to indicate the start of a trial and an event to indicate the end of a trial (Dalmaijer, 2016).

read_edf stores the data in the form of a list that contains values of all trials (one trial per index). Each trial is represented by a dictionary/dict (a composite data type in Python). Each dict has six keys: 'trackertime', 'time', 'x', 'y', 'size' and 'events'.

1. 'trackertime': Numpy array that contain absolute timestamps (time reported by eye tracker) of all samples
2. 'time': Numpy array that contains relative timestamps (start at 0 in every trial) of all samples
3. 'x': Numpy array that contains horizontal gaze position(in pixels) of all samples
4. 'y': Numpy array that contains vertical gaze position(in pixels) of all samples
5. 'size': Numpy array that contains pupil size of all samples
6. 'events': specify eye movements or messages. It refers to another dictionary/dict which has the following keys (each of these is a list of lists where the index of the first value of the list is 0):

a. 'Sfix' (fixation start): consists of fixation start time
   Sfix = ['start timestamp']
b. 'Efix' (fixation end): consists of fixation start time[0], fixation end time[1], fixation duration[2], average x position[3], average y position[4] and average pupil size[5]
   Efix = ['start timestamp', 'end timestamp', 'duration', 'average x pos', 'average y pos', 'average pupil size']
c. 'Sblk' (blink start): consists of blink start time
   Sblk = ['start timestamp']
d. 'Eblk' (blink end): consists of blink start time, blink end time and blink duration
   Eblk = ['start timestamp', 'end timestamp', 'duration']
e. 'Ssac' (saccade start): consists of saccade start time
   Ssac = ['start timestamp']

f. 'Esac' (saccade end): consists of saccade start time[0], saccade end time[1], saccade duration[2], saccade start x[3] and y position[4], saccade end x[5] and y position[6], saccade amplitude[7], saccade peak velocity[8]
   Esac = ['start timestamp', 'end timestamp', 'duration', 'start x', 'start y', 'end x', 'end y', 'amplitude', 'peak velocity']
g. 'msg' (messages): consists of logged messages (trial conditions, stimulus appearance, subject responses, etc) and their timestamps
   msg = ['Message 1', 'Message 2',...]

Depending upon the event (fixation, saccade, etc), the respective key and the list is extracted for a trial.

Eg: data[i]['events']['Efix'][0] extracts the fixation start, end time and fixation duration of the first fixation event of the i^{th} trial.

Similarly, data[i]['events']['Esac'][j] extracts saccade start and end time, saccade duration, saccade start x and y position, saccade end x and y position, amplitude and peak velocity of the j^{th} saccade of the i^{th} trial.

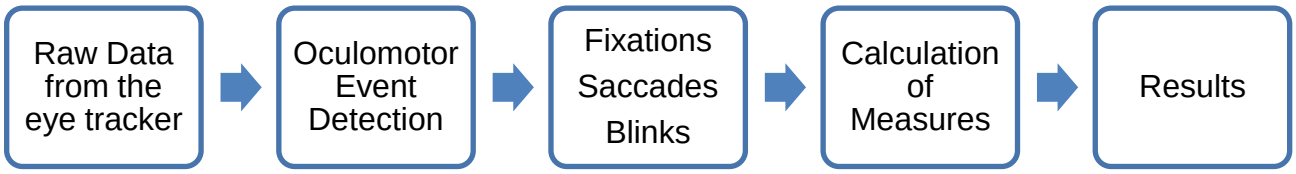


Figure 3: Workflow of the calculation of measures from eye tracking data

Figure 3 shows how measures for a particular event (can be fixations, saccades, etc) is calculated from the raw data. The eye tracking software (or toolbox) uses event detection algorithms to classify the gaze data into periods of fixation, saccade, blink, etc. Then, for each of these events, eye movement measures can be calculated.

Visualizations of gaze data can be either in the form of raw traces, fixation maps or heatmaps (Dalmaijer, 2016).

Raw trace: *draw_raw* function from the gazeplotter module of PyGaze analyser is used to plot raw trace. This function requires the following arguments: x coordinates of samples (extracted by calling data[trial_no]['x']), y coordinates of samples (extracted by calling data[trial_no]['y']) and the display size.

Fixation maps: plots fixation events for all trials. Each dot represents a fixation. It is created with the help of *draw_fixations* function from the gazeplotter module. It requires these arguments: list of fixation events (extracted by calling data[trial_no]['events']['Efix']), display size, *durationsize* (if set to True, dots will be sized according to fixation duration (i.e. longer the fixation duration, larger the dot will be, more time spent on that area)) and *durationcolour* (if set to True, longer fixations will have a 'hotter' color).

Heatmaps: represents denser fixations with hotter colors. They help to visualize which areas attract more attention than others. It is created with the help of *draw_fixations* function from the gazeplotter module. It requires these arguments: list of fixation events (extracted by calling data[trial_no]['events']['Efix']), display size, *durationweight* (if set to True, duration of fixations will be taken into account, with longer fixations being assigned more weight).

Variation of proportionate pupil size (pupil size during the presence of stimulus/ pupil size during baseline) in pro-saccade vs. anti-saccade trials: the timestamps and indices of the start of the baseline (no target) and appearance of the target stimulus were calculated. Pupil size during the baseline and presence of the target (data[trial_no]['size'][t1:t2], where t1 and t2 represent the start and end indices of each period) is extracted. Since pupil size changes over time, proportionate change in pupil size is calculated which is the ratio of pupil size during the presence of the stimulus divided by the median pupil size during the baseline period. This reflects the relative increase or decrease in pupil size during a trial. This is calculated for every trial and averaged separately over prosaccade and antisaccade trials. Similarly, we also calculated the proportionate pupil size separately for target only trials and target + distractor trials (Fixation stability test).

2.3 Subjects:

Subjects consisted of healthy controls and patients with Schizophrenia. The patients were diagnosed according to the criteria from DSM-IV. A sample anti-saccade (N=3) and fixation stability data (N=7) were used to develop the methodology. We then tested the pipeline using the anti-saccade (15 healthy controls and 14 patients) and the fixation stability data (34 healthy controls and 35 patients). The subjects selected for analysis were matched for age.

The age range of the selected subjects was between 22-35 years. We had approximately considered equal distribution of genders in both the fixation stability and the anti-saccade data. The data had been acquired over a period of time by the lab students under the supervision of Dr. Venkatasubramanian. The schizophrenic patients were specifically the ones suffering from auditory verbal hallucinations and medications were given specific to the subject's condition.

2.4 Eye movement recordings and paradigms:

Eye tracking data was collected by trained doctors/students. Before beginning the experiment, the dominant eye of the subject was assessed using Dolman method (Cheng et al., 2004). The eye movement data was recorded using the subject's dominant eye. The task stimuli were presented on a 22-inch flat screen monitor (Viewsonic, 120 Hz) with a screen resolution of 1680×1050 pixels and it was placed 74.3 cm in front of the subject. EyeLink 1000 eye tracker (SR Research), with a sampling frequency of 1000 Hz, was used to acquire the eye tracking data. The subjects were instructed to restrict any physical movements during the experiment. Head movements were restrained using chin and forehead rest.

For the fixation stability test, subjects were instructed to maintain a steady gaze on a central 0.5° circular yellow target for 5 seconds and to ignore an identical flanking distractor target when present appearing either ±1.43° (near distractor) or ±2.86° (far distractor) of the fixation target. The target only (or no distractor) condition was shown first followed by the other four conditions (near distractor or far distractor) in a random order. Each condition was repeated twice with a total of 10 trials.

In the anti-saccade paradigm, each subject performed a total of 72 trials (24 prosaccade and 48 antisaccade trials in separate blocks). The stimulus appeared on a screen with a black background. The fixation and target stimulus consisted of a 0.3 cm diameter circle (green for prosaccade and red for antisaccade). Each trial began with the fixation stimulus (located at the center of the screen) for a random duration between 800 and 1200ms. After this random interval of either 800 or 1200ms, the fixation stimulus disappeared, and following a gap of 200ms, the target stimulus (green/red) appeared. The target appeared at 4 possible locations on the screen, ±6° and ±12° from the center and it remained for a duration of 1000ms. The subject was instructed, for a prosaccade trial, to look at the target (green) when it appeared and

for an antisaccade trial, to look at the mirror image location of the target (red) without looking directly at the target itself (Taylor and Hutton, 2009).

2.5 Processing of eye movement data:

For the fixation stability test, we excluded fixation events having a time period less than 40ms. We also excluded saccades having too small (<0.1°) or too large amplitudes (>100°) or those having too short or long duration (<10 ms or >300 ms). We also identified and excluded saccades moving either toward or away from outside of the screen. We also excluded fixations which were outside the screen or near the boundary of the screen. We identified and excluded data points where data were missing which correspond to blink periods and those within ± 50ms of the blink periods (likely to be artifacts associated with eyelid opening or closures during the blink). All of these were excluded before the calculation of the measures (Morita et al., 2017; Nyström and Holmqvist, 2010).

For the anti-saccade task, we excluded saccades having latencies either <80ms or >600ms because these would represent either anticipation of the target stimulus or the subject not paying sufficient attention to the task (van Zoest et al., 2004). We also excluded trials in which the first saccade was in the correct direction but the eye crossed over the midline and looked close to/at the target during the trial. We also excluded trials where the subject was looking out of the screen (thereby having saccades moving towards/away from the screen and having negative start/end values). We identified antisaccade trials as erroneous if the first saccade has a latency between 80 and 600ms but the saccade direction is towards the target. We identified erroneous antisaccade trials as error corrected if the first saccade was in the same direction as the target but the eye crossed over the midline and looked close to/at the mirror image position during the course of the trial.

2.6 Data analysis:

For the fixation stability test, we measured fixation frequency, mean fixation duration(ms), median fixation duration(ms), saccade frequency, saccadic amplitude(°), scanpath length(°), and BCEA for each trial. We then averaged each measure over the trials corresponding to target only (no distractor), near distractor and far distractor conditions respectively.

- Fixation frequency: number of fixations in a given trial
  length(data[i]['events']['Efix']) gives the number of fixations
- Saccade frequency: number of saccades in a given trial
  length(data[i]['events']['Esac']) gives the number of saccades
- Mean fixation duration: the averaged value of all fixation durations in a given trial. First, all fixation durations are extracted by calling (*data[i]['events']['Efix'][j][2]*) which is stored in a list. The list contains the duration of every fixation present in that trial. Then the mean of all the values in the list is calculated.
- Median fixation duration: median value of all fixation durations in a given trial. First, all fixation durations are extracted by calling (*data[i]['events']['Efix'][j][2]*) which is stored in a list. Then the median of all the values in the list is calculated.
- Saccadic amplitude: Mean of all saccade amplitudes in a given trial. It is extracted by calling *data[i]['events']['Esac'][j][7]* which provides the amplitude of every saccade and is stored in a list. Then the average of all the values in the list is calculated
- Scanpath length: Sum of all saccade amplitudes in a given trial. It is extracted by calling *data[i]['events']['Esac'][j][7]* which provides the amplitude of every saccade and is stored in a list. Then the sum of all the values in the list is calculated.
- BCEA: It was computed using the following equation (Steinman, 1965):

  $$BCEA = 2*k*\pi*\sigma_H*\sigma_V*(1-\rho^2)^{1/2} \quad - \ (1)$$

  where σ_H represents the standard deviation along the x direction, σ_V represents the standard deviation along the y direction, ρ represents the product-moment correlation of x and y position components. k depends upon the probability of a given point falling within an area, which is given by the following equation:

  $$P = 1 - e^{-k} \quad - \ (2)$$

  where e is the base of the natural logarithm. P value of 0.68 (k = 1.14) was used in the calculation of BCEA (Culham et al., 1993; Nachmias, 1959). Spurious data (like blinks) were excluded before the calculation of BCEA.

(Note: i refers to the trial number (i^{th} trial); j refers to the fixation/saccade number in that trial; 2 refers to the index number representing the duration of the j^{th} fixation of the i^{th} trial; 7 refers to the index number representing the amplitude and peak velocity of the j^{th} saccade of the i^{th} trial.)

For the anti-saccade task, we calculated the following measures: anti-saccade error percentage, latency, peak velocity and amplitude gain (of correct antisaccades) and final eye position error. The same measures were calculated for prosaccade trials as well. All of these performance measures (except antisaccade or prosaccade error percentage) were calculated for every correct antisaccade/prosaccade trial and then averaged over all correct trials.

- Anti-saccade error percentage: defined as the ratio of erroneous analyzable antisaccade trials to the total number of analyzable antisaccade trials.

  AS error % = (number of error corrected trials + number of error uncorrected trials) / (number of error corrected trials + number of error uncorrected trials + number of correct trials)
- Average Latency: mean (timestamp when the first saccade is initiated - timestamp when target stimulus appears)
- Average Peak velocity : mean (*data[i]['events']['Esac'][0][8]*)
- Amplitude gain: Amplitude of first saccade (*data[i]['events']['Esac'][0][7]*) / Amplitude of the target
- Final eye position error is defined as the absolute value of one minus position gain (ratio of final eye position to the desired saccade end position).

(Note: i refers to the trial number; 0 refers to the first saccade in the i^{th} trial; 7 and 8 refer to the index numbers representing the amplitude and peak velocity of the first saccade of the i^{th} trial.)

Figure 4 depicts the workflow of the developed methodology. The figure outlines the main steps involved in analysing the EyeLink eye tracking data in form of a flowchart.

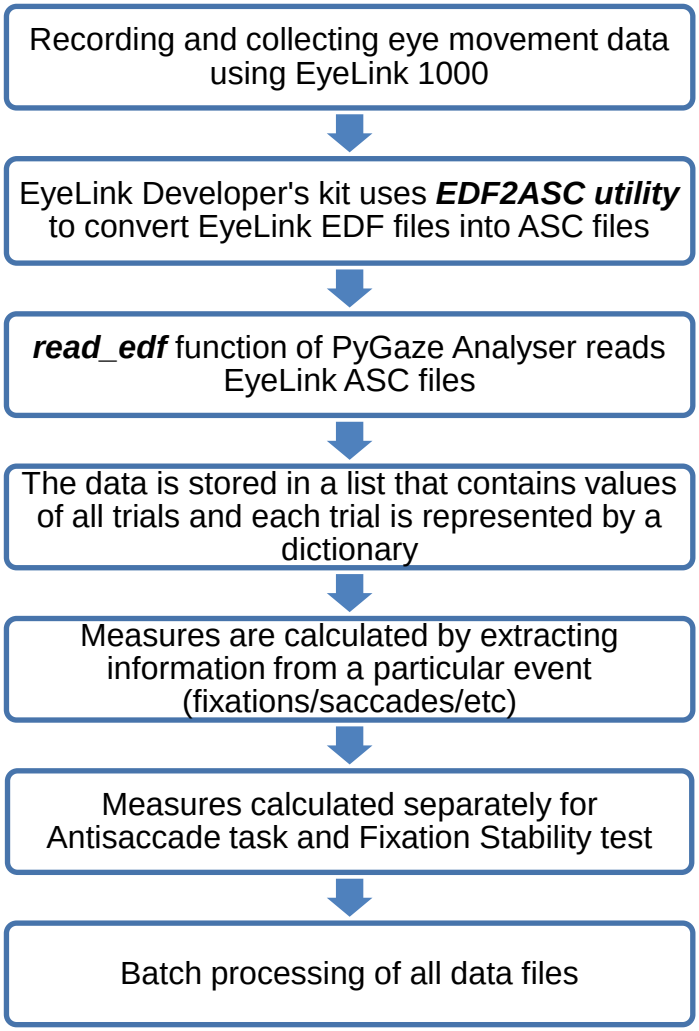


Figure 4: Workflow of the developed methodology using PyGaze.

2.7 Statistical analyses:

The statistical analyses (only for fixation stability test) were performed using SciPy, a free and open-source Python library. Most of the fixation stability test measures (fixation frequency, saccade frequency, average and median fixation duration, scanpath length, BCEA) were not normally distributed as assessed by Shapiro Wilk test and Anderson-Darling test ($p<0.05$). Hence Mann Whitney U test was used to compare the differences between the healthy controls and patients with schizophrenia for all the measures. The effect size for the fixation stability measures which were non-parametric was calculated using rank-biserial correlation(r_u) (Cohen, 1988; Cureton, 1956; Kerby, 2014; Wendt, 1972).

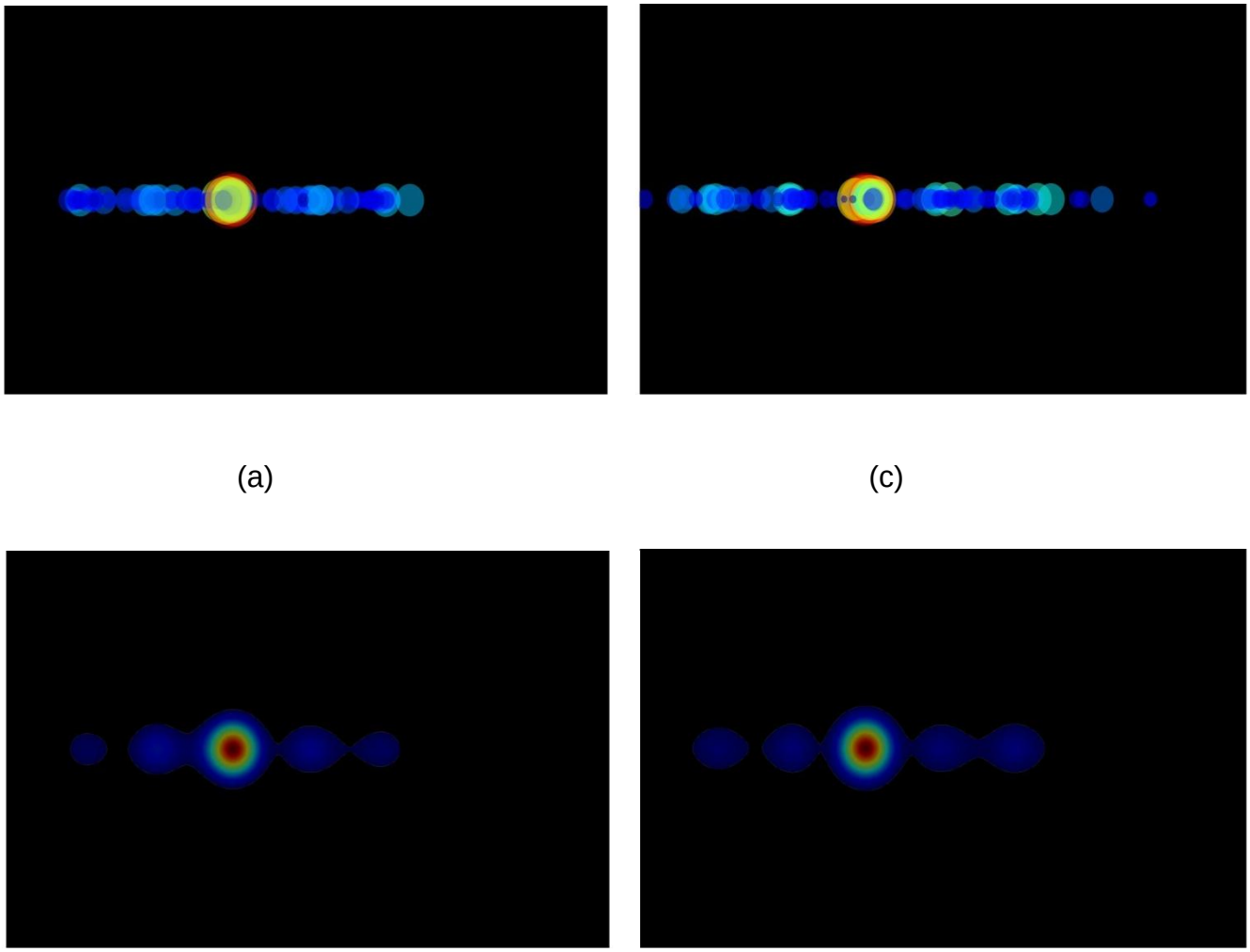
Two of the patients didn't make any correct response during the antisaccade trials due to which they were excluded from the calculation of AS measures. But their responses for the prosaccade trials were considered. The intraclass correlation coefficient (ICC) was calculated for each measure of the antisaccade paradigm.

Independent t-test was used to check if there was any significant difference in proportionate pupil size in the prosaccade and antisaccade trials as well as in the target only and target + distractor trials. Bonferroni corrected p-value was considered to assess significance.

CHAPTER 3

RESULTS

3.1 Visualizations for Antisaccade paradigm:



(a) (c)

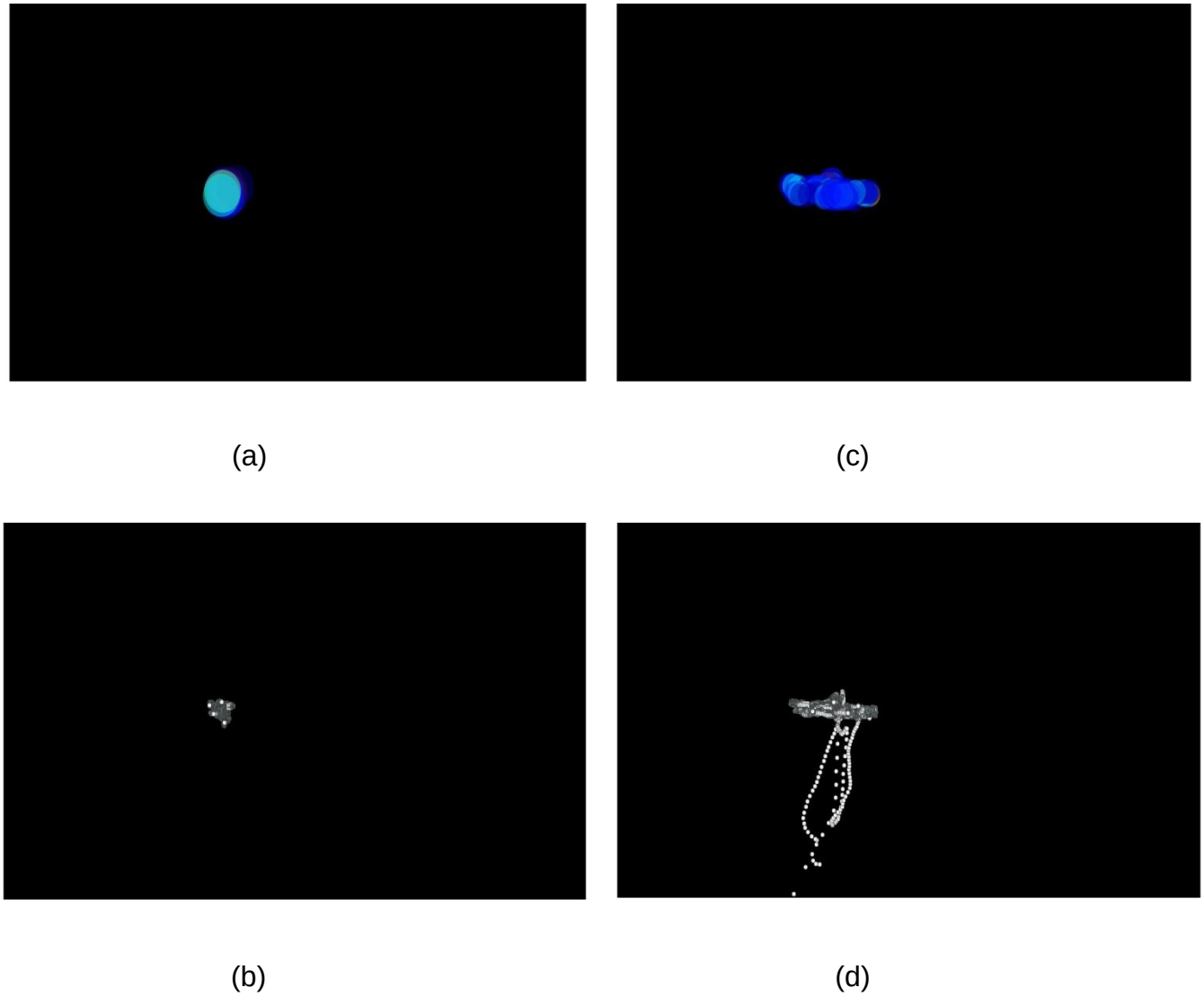
(b) (d)

Figure 5: Visualizations for Antisaccade paradigm. (a), (b) represents Fixation map and Heatmap for a sample healthy control; (c), (d) represents Fixation map and Heatmap for a sample patient

In Figure 5, (a) and (c) represents a fixation map, where each dot represents a fixation event. Larger the dot, longer is the duration of the fixation. The colors indicate the length of a fixation event, i.e. 'hotter' the color (of the dot), longer is the fixation duration. (b) and (d) represents a heatmap, where hotter colors represent denser fixations. Heatmap shows all the regions which have attracted the subject's

attention. In both (a) and (b), longer and denser fixations are seen at the center and shorter fixations are seen at the four target locations. In (c) and (d), longer and denser fixations are seen at the center and shorter fixations are seen at the four target locations. Fixation dots (events) in (c) are more scattered compared to fixation dots in (a).

3.2 Visualizations for Fixation Stability test:



(a) (c)

(b) (d)

Figure 6: Visualizations for Fixation Stability test. a, b represents Fixation map and Raw trace for a sample healthy control; c, d represents Fixation map and Raw trace for a sample patient

In Figure 6, (a) and (c) represents a fixation map, where each dot represents a fixation event. Larger the dot, longer is the duration of the fixation. The colors in the

fixation map indicate the length or duration of fixation events, i.e. 'hotter' colors represent longer fixations. (b) and (d) represents a raw trace, where each dot represents a gaze point. The raw trace shows all the regions that the subject has gazed during the task. In both (a) and (b), fixation is seen to be the highest at the center. But, in (c) and (d), fixation is seen to be more dispersed along x direction. In (d), the gaze points along y direction represent blinks.

3.3 Variation of Proportionate Pupil Size:

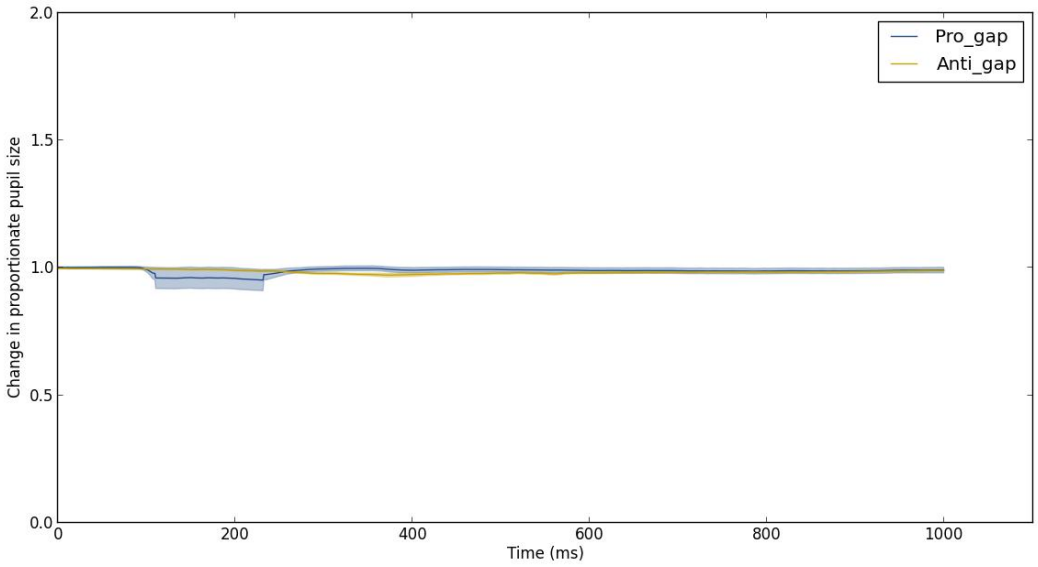


Figure 7: Variation of proportionate pupil size in Prosaccade vs. Antisaccade trials

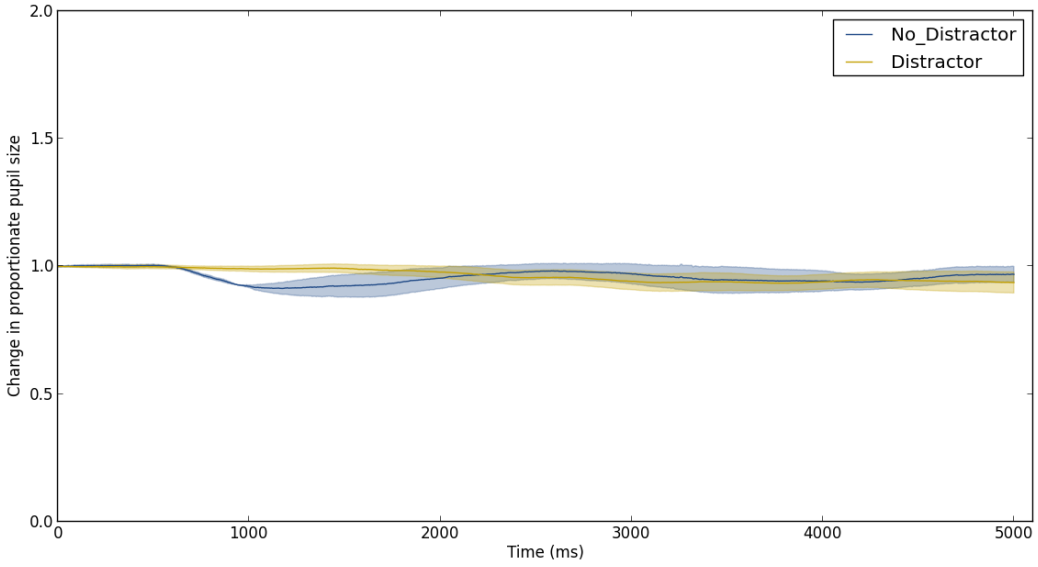


Figure 8: Variation of proportionate pupil size in No Distractor vs. Distractor trials

Figure 7 and 8 represent variation of proportionate pupil size along the length of a trial in AS paradigm and FS test. The lines indicate the averaged proportionate pupil size for a particular condition. Shading around the lines indicates the standard error of the mean (SEM) and the grey shading, if present, indicates where the two conditions differ significantly from each other (Bonferroni corrected, point-wise related t-tests were performed).

In Fig 7, there is no grey shading throughout the length of the trial which indicates that the change in proportionate pupil size means (of both the conditions) aren't significantly different. Therefore, there is no significant difference/variation in proportionate pupil size when compared between the prosaccade and antisaccade trials. Similarly, in Fig 8, grey shading isn't observed throughout the length of the trial, due to which there is no significant variation in proportionate pupil size when compared between no distractor (target only) and distractor conditions.

3.4 Antisaccade paradigm measures:

Intraclass correlation was calculated to check the relative consistency or reproducibility of the measures calculated using EyeLink data viewer (Subramaniam et al., 2018) and the developed methodology respectively. Intraclass correlation was calculated for both the antisaccade and prosaccade measures. Intraclass correlation coefficient (ICC) was calculated for all the antisaccade paradigm measures of 5 subjects (chosen randomly from 15 healthy controls and 14 patients). ICC estimates were calculated using the consistency, two-way mixed-effects model. The performance measures for each subject was calculated, which was then used to estimate ICC.

Table 3 shows the eye movement measures calculated for the antisaccade paradigm (for 5 subjects) using the data viewer and the developed methodology. An excellent degree of reliability with ICC equal to 1.0 was found between the results from the two methods. The mean and the standard deviation calculated for each measure were also found to be in complete agreement. The average (and single) measure ICC was 1.0 with a 95% confidence interval. Then, each performance measure was also calculated for all healthy controls (n = 15) and schizophrenic patients (n = 14).

	EyeLink Data Viewer (n = 5)	Developed methodology* (n = 5)
AS error %**	68.69 ± 23.41	68.69 ± 23.41
AS Latency** (ms)	233.84 ± 144.17	233.84 ± 144.17
AS Peak velocity** (deg/sec)	213.16 ± 167.18	213.28 ± 167.2
AS Amplitude gain**	0.66 ± 0.62	0.66 ± 0.62
AS Position error**	0.41 ± 0.32	0.41 ± 0.32
PS error %**	0 ± 0	0 ± 0
PS Latency** (ms)	143.93 ± 15.3	143.93 ± 15.3
PS Peak velocity** (deg/sec)	347.49 ± 54.08	347.54 ± 54.12
PS Amplitude gain**	0.87 ± 0.09	0.87 ± 0.09
PS Position error**	0.17 ± 0.09	0.17 ± 0.09

Table 3: Eye movement measures for Antisaccade paradigm. The measures are calculated using both the data viewer and the developed methodology.
(* using PyGaze; ** ICC equals 1.0)

3.5 Fixation Stability test measures:

Table 4 shows the eye movement measures calculated for the fixation stability test. The measures, which have $p < 0.05$ for each condition (i.e. statistically significant), are highlighted in bold. The measures were calculated separately for target only (i.e. no distractor), near distractor and far distractor conditions. For each measure, Mann Whitney U test and r_u (effect size for non-parametric measures) were calculated. n_1 and n_2 refers to the number of healthy controls and patients with schizophrenia respectively.

None of the eye movement measures in Target only (No Distractor) condition were found to be statistically significant.

In **near distractor condition**, fixation frequency ($U = 382.5$, $n_1 = 34$, $n_2 = 35$, $P = .01$ two-tailed, $r_u = 0.357$), mean fixation duration ($U = 407.5$, $n_1 = 34$, $n_2 = 35$, $P = .02$ two-tailed, $r_u = 0.316$), median fixation duration ($U = 367$, $n_1 = 34$, $n_2 = 35$, $P =$

.006 two-tailed, r_u = 0.383), saccade frequency (U = 398.5, n_1 = 34, n_2 = 35, *P = .02* two-tailed, r_u = 0.33), mean saccadic amplitude (U = 394, n_1 = 34, n_2 = 35, *P = .02* two-tailed, r_u = 0.338), and scanpath length (U = 383.5, n_1 = 34, n_2 = 35, *P = .01* two-tailed, r_u = 0.355) were found to be statistically significant ($p < 0.05$). All these measures have an intermediate effect size. BCEA (U = 545.8, n_1 = 34, n_2 = 35, *P = .56*) did not reach statistical significance.

In **far distractor condition**, fixation frequency (U = 396, n_1 = 34, n_2 = 35, *P = .02* two-tailed, r_u = 0.334), mean fixation duration (U = 421, n_1 = 34, n_2 = 35, *P = .04* two-tailed, r_u = 0.292), median fixation duration (U = 412, n_1 = 34, n_2 = 35, *P = .03* two-tailed, r_u = 0.308), saccade frequency (U = 386.5, n_1 = 34, n_2 = 35, *P = .01* two-tailed, r_u = 0.35), mean saccadic amplitude (U = 355.5, n_1 = 34, n_2 = 35, *P = .004* two-tailed, r_u = 0.403), and scanpath length (U = 351, n_1 = 34, n_2 = 35, *P = .004* two-tailed, r_u = 0.41) were found to be statistically significant ($p < 0.05$). All these measures have an intermediate effect size. BCEA (U = 503, n_1 = 34, n_2 = 35, *P = .27*) did not reach statistical significance.

	Healthy Controls (n = 34)	Patients with Schizophrenia (n =35)	r_u	U statistic	p-value
	Mean ± SD	Mean ± SD			
Target only (No Distractor) condition					
Fixation Frequency	5.3 ± 3.5	5.8 ± 2.4	0.215	467.0	0.126
Mean Fixation Duration (ms)	1771.4 ± 1390.9	1170.9 ± 711.6	0.205	473.0	0.144
Median Fixation Duration (ms)	1656.4 ± 1425.8	1019.7 ± 760.2	0.222	463.0	0.114
Saccade Frequency	3.5 ± 3.2	3.4 ± 2.3	0.067	555.0	0.634
Mean Saccadic Amplitude (deg)	0.47 ± 0.37	0.57 ± 0.30	0.213	468.5	0.13
Scanpath Length (deg)	2.10 ± 2.27	2.18 ± 1.67	0.136	514.0	0.334
BCEA (min arc^2)	477.2 ± 586.4	829.9 ± 1612.9	0.061	559.0	0.67
Target + Near Distractor condition					
Fixation Frequency	**5.7 ± 3.7**	**7.4 ± 3.0**	**0.357**	**382.5**	**0.01**
Mean Fixation Duration (ms)	**1679.2 ± 1264.5**	**984.3 ± 898.1**	**0.316**	**405.0**	**0.022**
Median Fixation Duration (ms)	**1522.7 ± 1312.4**	**764.8 ± 912.0**	**0.383**	**367.0**	**0.006**
Saccade Frequency	**3.8 ± 3.5**	**5.0 ± 2.6**	**0.33**	**398.5**	**0.018**
Mean Saccadic Amplitude (deg)	**0.58 ± 0.35**	**0.77 ± 0.31**	**0.338**	**394.0**	**0.016**
Scanpath Length (deg)	**3.24 ± 3.71**	**4.40 ± 3.02**	**0.355**	**383.5**	**0.012**
BCEA (min arc^2)	956.8 ± 1660.5	1795.3 ± 4656.7	0.083	545.8	0.556
Target + Far Distractor condition					
Fixation Frequency	**5.7 ± 3.9**	**7.3 ± 3.1**	**0.334**	**396.0**	**0.018**
Mean Fixation Duration (ms)	**1626.5 ± 1171.7**	**1013.7 ± 786.4**	**0.292**	**421.0**	**0.038**
Median Fixation Duration (ms)	**1426.2 ± 1147.8**	**842.6 ± 837.8**	**0.308**	**412.0**	**0.028**
Saccade Frequency	**3.6 ± 3.6**	**5.1 ± 3.0**	**0.35**	**386.5**	**0.012**
Mean Saccadic Amplitude (deg)	**0.68 ± 0.47**	**1.02 ± 0.46**	**0.403**	**355.5**	**0.004**
Scanpath Length (deg)	**3.99 ± 5.60**	**6.13 ± 4.41**	**0.41**	**351.0**	**0.004**
BCEA (min arc^2)	953.1 ± 1257.9	1852.8 ±3338.9	0.155	503.0	0.272

Table 4: Eye movement measures for Fixation Stability Test

CHAPTER 4

DISCUSSION

A new methodology was developed to analyse EyeLink eye tracking data using PyGaze, an open-source Python toolbox. PyGaze was selected since it was compatible with multiple operating systems and multiple eye tracker brands like EyeLink, SMI, etc. Also, it supported data acquisition, visualization, and analysis (Dalmaijer et al., 2014; Dalmaijer, 2016). It allowed user flexibility and the ease of handling everything on a single platform. The scripts could be shared and accessed across groups. All the scripts for the calculation of performance measures were coded in Python, an open-source programming language. The eye tracking data was analysed using batch processing. The data files from an eye tracker, if converted into ASC format (with the required parameters and format) can be analysed by this methodology.

The visualizations for both the paradigms can be more useful in qualitative rather than quantitative analysis since not all visualizations provide information as to whether a given subject is a healthy control or a patient. No significant variation in proportionate pupil size was observed along the length of a trial in both the tasks. Most of the measures of the fixation stability test (near and far distractor condition) were found to be statistically significant ($p < 0.05$). The fixation stability measures which were found to be statistically significant is consistent with the results of other studies (Benson et al., 2012; Miura et al., 2014; Morita et al., 2017). Excellent inter-method reliability with the intraclass correlation coefficient (ICC) equal to 1 was found between the results from the data viewer and the developed methodology for each of the antisaccade paradigm measures. The measures calculated (by the two methods) were in complete agreement, which confirms that our methodology is reliable and can be used to analyse eye tracking data.

BCEA was mainly used to assess fixation stability in patients with macular degeneration (Crossland and Rubin, 2002; Crossland et al., 2004). Since studies had shown that patients with Schizophrenia were poorer at maintaining fixation and had difficulties in inhibiting eye movements towards the distractor target (Benson et al., 2012), we expected BCEA could be a potential biomarker used to discriminate between controls and patients. But, surprisingly it didn't show any statistical significance. It might be possible that BCEA wasn't significant due to a smaller

sample size. Some studies have shown fixation frequency, fixation duration and saccade amplitude for no distractor condition to be statistically significant (Benson et al., 2012) but in our case, they didn't reach statistical significance which may be due to smaller sample size.

The measures calculated using the developed methodology is in optimal concordance with that calculated using the data viewer. However, one has to take into account that the measures calculated can be influenced by various parameters like screen resolution, pixel density, target features, etc. Eye movement measures from other eye-tracking paradigms can be analysed using the developed methodology.

Since no variation in proportionate pupil size was observed in the antisaccade paradigm, one can check whether there is variation in pupil size before and after the erroneous trials. Also, one has to take into account several factors like left or right dominant eye being recorded, near or far target location, the appearance of the target either to the left or right, prosaccade or antisaccade trials, etc to observe any variation in pupil size. The subjects, whose eye tracking data were used for analysis, were matched only with respect to age. Others demographic factors like education level, IQ, sex, etc should also be matched before analysis (Benson et al., 2012; Morita et al., 2017). These performance measures can be compared among male and females and can be used to let one know who is at a higher risk. These measures can also be calculated for the first degree relatives of the patients who are at a higher risk of developing Schizophrenia. These measures can be combined with features from other eye-tracking paradigms and be used to build classifier models (Benson et al., 2012). These measures can be used for other psychiatric disorders, which would be required to conclude whether these measures are specific to Schizophrenia.

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