

2021

Detection of delirium through eye-tracking methods

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

DETECTION OF DELIRIUM THROUGH EYE-TRACKING METHODS

by

WINNIE CHING

B.S., University of Massachusetts Amherst, 2018

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2021

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Approved by

First Reader

David Flynn, M.S.
Assistant Director of Library and Information Management Education
Boston University, School of Medicine

Second Reader

Anoopum Gupta, M.D., Ph.D.
Assistant in Neurology
Massachusetts General Hospital

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ABSTRACT

Previous research has shown increased saccade latencies in patients with Alzheimer's disease and mild cognitive impairment; however, this is not well-understood in patients with delirium. The present study investigates eye-tracking metrics to evaluate the feasibility of using eye-tracking to discern delirious patients from disease control patients. We recruited 24 participants from the inpatient and intensive care units (ICU) at Massachusetts General Hospital (MGH) and assessed for delirium via CAM-S, a screening tool for delirium. Participants were instructed to follow a dot stimulus as it moves across the laptop screen as their eye movements were simultaneously tracked by a Tobii Pro Fusion eye-tracker. Our experimental paradigm involved gap saccades (central fixation extinguishes before the centrifugal target appears), overlap saccades (central fixation remains after centrifugal target onset), horizontal smooth pursuit, and circular smooth pursuit tasks. The eye-tracking metrics discussed in this study are the calibration and validation accuracies, saccade latencies and total target gaze duration. Our eye-tracking method was able to capture subjects' gaze direction and path, but further research is needed to draw strong conclusions about the feasibility to detect oculomotor abnormalities in patients with delirium.

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LIST OF ABBREVIATIONS

ADHD.....	Attentional deficit and hyperactivity disorder
CAM.....	Confusion Assessment Method
CV.....	Coefficient of variation
DSM.....	Diagnostic Statistical Manual of Mental Disorders, fifth edition
EEG.....	Electroencephalography
ICDSC.....	Intensive Care Delirium Screening Checklist
ICU.....	Intensive care unit
MGH.....	Massachusetts General Hospital
mTBI.....	Mild traumatic brain injury
SD.....	Standard deviation

INTRODUCTION

What is Delirium?

Delirium is the acute onset of fluctuating mental status and disturbance in attention and may also present itself with other cognitive deficits such as memory impairment or disorientation. The mental status seen in delirious patients changes rapidly, occurs over several hours to days, and often fluctuates. According to the Diagnostic Statistical Manual of Mental Disorders, fifth edition (DSM-5), the diagnostic criteria for delirium includes an interruption in attention and awareness that develops over a short period of time, and another disturbance in cognition (Lawlor & Bush, 2014). The presentation of the delirious state can vary widely thus complicating the diagnostic and screening process and leaving the pathophysiological processes of delirium poorly understood. In addition, delirium is multifactorial; its causes may come from many different origins and can be metabolic, neurologic, or environmental in nature (Tulebaev, Inouye, & Fong, 2009). This often results in misdiagnosing or underdiagnosing delirium in patients.

Prevalence of Delirium

While delirium is not common in the general community, the incidence of delirium in a hospital setting may range widely depending on the type of care patients are receiving and their risk factors. Researchers found the incidence of delirium in patients

receiving major elective surgery ranged from 15 to 25% and increased to 50% after high-risk procedures such as joint replacement surgery and cardiac surgery (Marcantonio & Solomon, 2017). The notable risk factors include dementia and advanced age , which contribute to the high occurrence of delirium. The incidence of delirium in elderly patients admitted to the ICU then increases to about 70-87% (Tulebaev, Inouye, & Fong, 2009). The diverse etiologies and presentation of delirium in addition to its high rate in ICUs calls for improved screening and detection (Lawlor & Bush, 2014). Furthermore, many hospital staff who routinely provide care for delirious patients lack the specific training and knowledge to properly assess the patient. With more objective and accurate screening for delirium, we may be able to offset the negative consequences of misdiagnosing delirium such as increase in the length of hospital stay, cognitive impairment, and mortality that patients face.

Available Tools for Delirium Assessment

In the ICU, the common tools used to detect delirium include the Confusion Assessment Method (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). Both screening tools are designed for patients staying in the hospital ICU. The CAM-ICU assesses for the presence of acute onset and fluctuating course, altered consciousness, inattentiveness, and disorganized thinking. The presence of acute onset and fluctuating course and inattention along with the presence of either altered level of consciousness or disorganized thinking results in a positive CAM-ICU assessment, which

reflects the DSM-5 criteria for delirium. The ICDSC's scale is designed for patients who have limited ability to communicate such as those who have been intubated. This tool assesses patients' level of consciousness, hallucinations, disorientation, psychomotor activity, inappropriate speech, sleep quality, inattentiveness, and fluctuation of symptoms. The score for the ICDSC ranges from 0 to 8; scores of 4 or higher is indicative of delirium. (Boettger, et al., 2018). CAM-ICU has a sensitivity of 80% and specificity of 95.9%, while ICDSC has a sensitivity of 74% and specificity of 81.9% (Gusmao-Flores, Salluh, Chalhub, & Quarantini, 2012). The CAM- ICU offers the higher sensitivity and specificity in diagnosing delirium.

Because delirium is the result of many potential underlying conditions and is insufficiently understood, there are no biomarkers that clinicians currently use to diagnose delirium. Ultimately, diagnostic tools heavily rely on medical history, observation, and assessment of cognition (Tieges, Evans, Neufeld, & MacLulich, 2018). The CAM-S, like the CAM-ICU, can assess for the diagnostic features of delirium. Unlike the CAM-ICU, CAM-S can provide more insight on patient's level of severity in each delirium feature. The CAM-S long form contains 10 items with a score range of 0 to 19 (19 is most severe). The 10 items included the acute onset or symptom fluctuation, altered level of consciousness, altered sleep-wake cycle, disorientation, inattention, disorganized thinking, perceptual disturbances, psychomotor agitation, psychomotor retardation, and memory deficits. Each feature is scored 0-2, except for the acute onset or fluctuating course which is scored 0-1. (Inouye, et al., 2014). Because of the limited tools

available for delirium detection, there is a demand for more accurate and objective tests to assess for delirium.

Eye-tracking for Detecting Attentional Deficits

Eye-tracking research has been around for centuries and the need for accurate measures of eye gaze has led to the advancement in eye-tracking technology. In the 19th century, scientists such as French ophthalmologist, Louis Émile Javal, studied eye movements without modern day technology by regular observation. Through these observations, Javal noticed that subjects' eye movements were not continuous as they read through lines of text and proposed that the reading process involves brief, abrupt eye movements followed by pauses or fixations. Javal then introduced the French term "saccades" to describe these short eye movements, which translates to "jerks" in English. His method for counting saccades involved attaching a microphone to subjects' upper eyelid and counting each time he heard the readers' eyes jerk (Płużyczka, 2018; Wade, 2010). By the 20th century, eye-tracking technology began to emerge when Edmund Huey invented contact lenses that connected to an aluminum indicator that shows the participants' eye movements. However, this device was incredibly invasive, which lead Raymond Dodge to design a photographic eye-tracker that did not require attachment to the eye to capture its movements (Wade, 2010). Through the centuries, eye-tracking devices have been refined and advanced and have truly made an impact on the way researchers study eye movements.

Saccades

Recently, studies have promisingly demonstrated the potential in eye-tracking data to serve as biomarkers for neurological conditions. By extracting and analyzing the quantitative gaze data, researchers notice differences in the data between patients with attention deficit hyperactivity disorder (ADHD) and control participants (Terao, Fukuda, & Hikosaka, 2017). Inattention is a core feature of delirium and can be captured through eye-tracking in several ways. Since Javal's introduction to saccades, saccades have often been used by researchers to understand not only motor function, but also cognition (Leigh & Kennard, 2004). Cognitively healthy individuals are able to disengage their attention towards an irrelevant stimulus and shift their attention towards the target sooner than individuals with attentional deficits, especially patients with Alzheimer's disease (Malhotra, 2019). The gap and overlap saccade paradigms have been studied for its ability to assess this attentional disengagement in this patient population (Crawford, et al., 2013). In the gap saccade paradigm, there is a brief 'gap' in time between the removal of the central fixation and the onset of the new peripheral target. In the overlap saccade paradigm, the central fixation stays on as the new peripheral target appears and the presentation of the two stimuli 'overlaps' for a short period before the central fixation disappears. The measure of the gap effect is the difference in saccade latencies between the gap and overlap saccades. Because the overlap saccade requires greater effort for an individual to disengage attention from the central fixation, subjects may require more time thus the overlap saccade latency tends to be greater than the gap saccade latency. In

patients with Alzheimer's disease, it was found that their gap effect is greater than healthy controls (Yang, Wang, Su, Xiao, & Kapoula, 2013). The subjects' ability or inability to attentionally disengage from a non-target stimulus and subsequently shift attention towards the target stimulus may provide useful information about their cognitive functioning in attention-impaired conditions such as delirium.

Smooth Pursuit

Another method to assess attention by eye-tracking is through a smooth pursuit paradigm. According to Contreras et al. (2008), smooth pursuit eye movement is heavily dependent on attentional processes. The smooth pursuit paradigm involves a target that moves continuously across a distance without interruption and this movement often prompts subjects to follow the target with their eyes. The task requires subjects to sustain their attention in order to follow the target's continuous path, therefore, weakened attention during this task would disrupt the subject's tracking of the target. The neurons in the middle and superior temporal areas are activated by visual motion stimulation; moreover, activation is enhanced when subjects are asked to pay attention to a certain attribute of the path of the target. Studies have shown that visual search tasks are performed more accurately and quickly when targets are being pursued than those that are not due to the increased attentional efforts (Van Donkelaar & Drew, 2002). The smooth pursuit task has been found to be suitable for early detection of cognitive deficits in the onset of dementia, especially Alzheimer's disease (Müller, Richter, Weisbrod, &

Klingberg, 1991). In addition, in other conditions where attention is impaired such as schizophrenia and ADHD, smooth pursuit is disrupted (Van Donkelaar & Drew, 2002). Attentional deficits have also been captured by horizontal and circular smooth pursuit paradigms in patients with mild traumatic brain injury (mTBI), where the connection between the frontal cortex and cerebellum is damaged. Furthermore, smooth pursuit performance in patients with mTBI is highly variable (Contreras, Ghajar, Bahar, & Suh, 2011; Maruta et al., 2010; Maruta et al., 2017). It is also important to note that attention may vary over time and tracking subjects' gaze following a continuous trajectory with their eyes may provide useful information about their attention over the course of the task (Maruta et al., 2010). Therefore, we believe that the detection of interrupted smooth pursuit eye movements by eye-tracking may be an appropriate assessment for other cognitively impairing conditions such as delirium. The assessment of how well the participant can stay engaged with the moving target can be further explored by examining the total duration of the eye's gaze on the target.

Many eye-tracking studies have examined attentional deficits in conditions such as Alzheimer's disease, schizophrenia, and ADHD but it is less studied in delirium. To address the current need to develop accurate, non-invasive tools to detect delirium in patients hospitalized in the ICU, the present study utilized the CAM-S assessment to assess patients for delirium severity in conjunction with eye-tracking. We hope to provide valuable information about the practicality of eye-tracking techniques to detect delirium features in hospitalized patients with varying levels of severity.

GOALS

Studies have demonstrated high incidence of delirium in patients in various settings of the hospital. Delirium often occurs in patients staying in the ICU and many of these cases are left misdiagnosed or underdiagnosed due to its complexity and multifactorial causes. The tools available for delirium detection, such as the CAM-S test, require the scorer's subjective input to assess the severity of each characteristic of the condition. Thus, researchers recognize the need for objective measures to accurately diagnose delirium to prevent negative patient outcomes such as prolonged hospital stays and increased cognitive impairment.

At this time, there are limited screening tests to assess for the condition and we recognize the current need for more accurate, accessible delirium assessments. This paper's overall goal is to discuss the feasibility of eye-tracking as an objective method to assess for delirium features.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

All study protocols were approved by the Partners Healthcare Institutional Review Board. Prior to beginning the study, verbal consent was acquired for all participants from either the participant or his or her surrogate. An information sheet with further details about the study was provided to the participants.

Participant Selection

Twenty-four participants were recruited from the inpatient and intensive care units at the Massachusetts General Hospital. The disease control group consisted of 16 participants (age range = 22-77; mean = 56.25; SD = ± 15.24 ; male $n = 12$; female $n = 4$; see Table 1) who had negative CAM-S assessments with a score range of 0-4. The delirium group consisted of 8 participants who had positive CAM-S assessments; four of these participants completed the oculomotor tasks (age range = 23-63; mean = 47.75; SD = ± 17.61 ; male $n = 2$; female $n = 2$; see Table 2) and had a CAM-S score range of 4-11. Four participants in the delirium group with a CAM-S score range of 8-14 were unable to complete the oculomotor tasks due to sleepiness, confusion, and the eye-tracker's inability to detect subjects' eyes. Patients' charts were reviewed, and their primary diagnosis was documented. In order for a participant to meet the inclusion criteria, they needed to be older than 18 years of age and undergoing an electroencephalography

(EEG) recording to assess brain activity. Patients were excluded from the study if deemed unsuitable for participation by the research or medical care team due to medical, legal, social, or interpersonal issues that compromised the study or the routine care of patients.

Table 1: Demographics and CAM-S Score of the Disease Control Group. The mean and standard deviation of age and CAM-S score were defined.

Disease Control Subjects	Age	CAM-S score	Sex
1	68	0	Male
2	57	1	Male
3	73	1	Male
4	22	0	Female
5	62	3	Male
6	69	3	Male
7	77	2	Female
8	41	0	Male
9	43	2	Male
10	39	1	Female
11	59	2	Female
12	65	0	Male
13	41	1	Male
14	65	4	Male
15	51	3	Male
16	68	2	Male
Mean	56.25	1.5625	
SD	15.2381	1.2633	

Table 2: Demographics and CAM-S Score of the Delirium Group. The mean and standard deviation of age and CAM-S score were defined.

Delirium Subjects	Age	CAM-S score	Sex
1	57	8	Male
2	23	10	Male
3	48	11	Female
4	63	4	Female
Mean	47.75	8.25	
SD	17.6137	3.0957	

Apparatus

Eye movements were binocularly captured by the Tobii Pro Fusion eye-tracker (Tobii Pro AB, Stockholm) at a 250 Hz sampling rate and saved to the Tobii Pro Lab software (Tobii Pro AB, Stockholm). The eye-tracker was mounted on a 15.6-inch Lenovo Thinkpad P1 Gen 2 laptop (Lenovo, Sha Tin, HK) with a 1920 x 1080 pixel resolution display, where the visual stimuli were presented. The 15.6-inch ASUS ZenScreen MB16ACE monitor was attached to the laptop for the research assistant to ensure that participants were engaging in the tasks asked of them. The apparatus was set 65 centimeters in front of the participant as the participant sat comfortably in the hospital bed as shown in Figure 1. To ensure accurate eye gaze capture, calibration and validation were performed at the beginning. For these procedures, participants were asked to follow

a gray dot as it moves around the laptop screen at five different positions. In the coordinate system, the top left of the screen is (0, 0) and the bottom right of the screen is (1, 1). The dot landed on positions (0.1, 0.1), (0.5, 0.5), (0.9, 0.1), (0.1, 0.9), and (0.9,0.9) for the calibration procedure and landed on positions (0.3, 0.3), (0.3, 0.7), (0.7, 0.3), and (0.7, 0.7) for the validation procedure. The order of these positions was randomized by the Tobii Pro system.

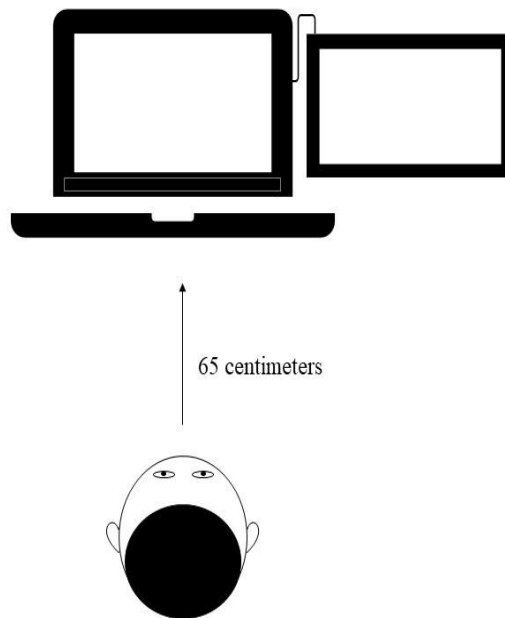


Figure 1. Experimental Apparatus. Patients were sitting comfortably on the MGH hospital bed and the laptop and external monitor were set 65 centimeters in front of the patient on the overbed table.

Visual Stimuli

Gap Overlap Saccade Task

The gap overlap saccade task included both 12 gap saccade and 12 overlap saccade trials and these trials occurred randomly. The circular, white target subtended an angle of 0.7° on a black background. Each trial began with a central fixation that was presented for a random period between 1500 and 2000 milliseconds. In the gap saccade trials, the central fixation was followed by a 200-millisecond gap which consisted of a blank screen before onset of the eccentric target and the target remained for 1500 milliseconds. Figure 2a demonstrates a right gap saccade trial. In the overlap saccade trials, the central fixation remains on the screen as the eccentric target appears and overlaps for 200 milliseconds before disappearing from the screen. The target remained for another 1500 milliseconds as demonstrated in Figure 2b. All eccentric targets were either 10° to the left or right and occurred at random. Participants were instructed to follow the dot with their eyes without moving their head.

Horizontal Smooth Pursuit Task

The circular, white target subtended an angle of 0.7° on a black background on the Lenovo laptop screen. The target moved sinusoidally left and right at 0.2 Hz. Participants were instructed to follow the dot with their eyes without moving their head as the target moved continuously left and right with 10° maximal eccentricity.

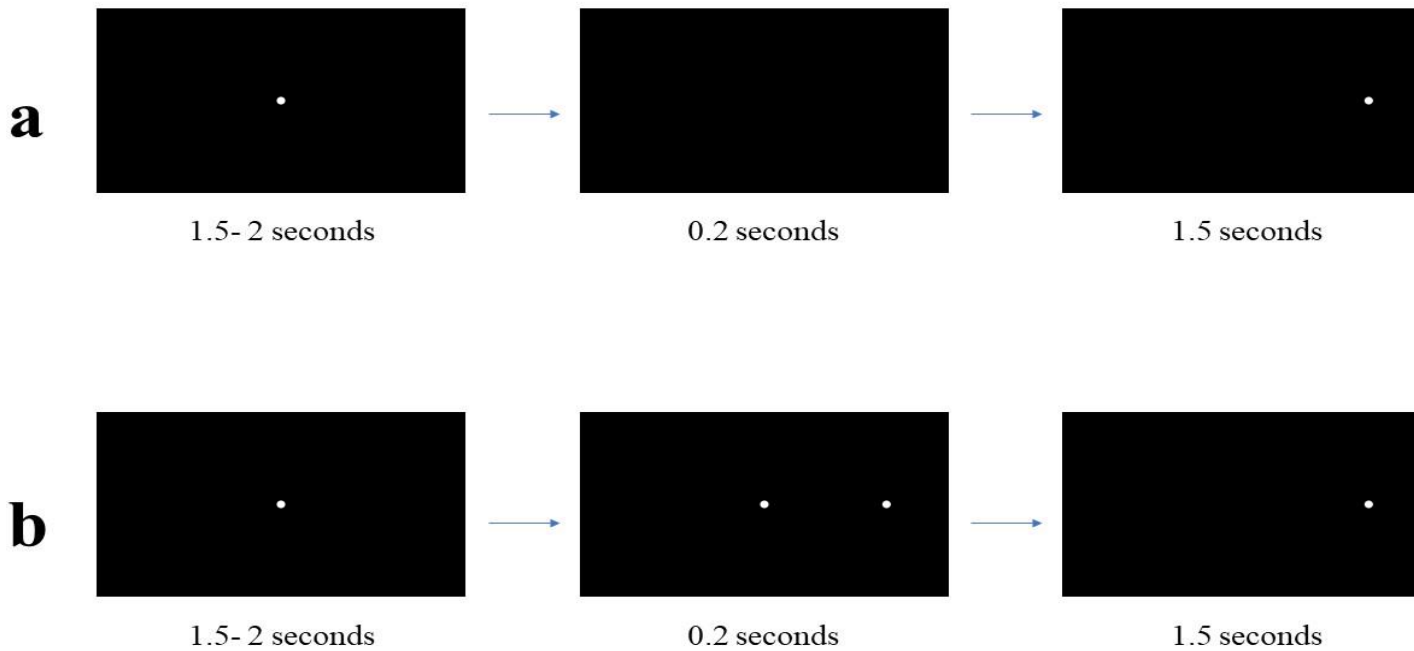


Figure 2. Gap and Overlap Saccade Trials. a) Gap Saccade. The central fixation appears for a random period between 1500 and 2000 milliseconds and is followed by a blank screen for 200 milliseconds. Finally, the target appears for 1500 milliseconds. b) Overlap Saccade. The central fixation also appears for a random period between 1500 and 2000 milliseconds and stays on the screen, overlapping with the target for 200 milliseconds. The target remains for an additional 1500 milliseconds on its own.

Circular Smooth Pursuit Task

The circular, white target subtended a visual angle of 0.7° on a black background and moved clockwise in a circular trajectory with radius of 5° of visual angle at 0.4 Hz. The participants were asked to follow the dot their eyes without moving their head as the target moved continuously in a circular path.

Procedure

The research assistant assessed subjects for delirium via CAM-S and assessed for any challenges that the subject may face during the study session and mitigated those challenges. The CAM-S assessment was followed by the calibration and validation procedure discussed earlier, then the gap overlap saccade, horizontal smooth pursuit, and the circular smooth pursuit task. Both the horizontal and circular smooth pursuit tasks lasted 30 seconds each. Prior to each task, an instruction page was presented and participants were instructed to follow the dot with their eyes without moving their head.

Analysis

Data were analyzed using the MATLAB Software. The eye-tracking metrics obtained were calibration and validation accuracies, saccade latencies and total gaze duration on the smooth pursuit target.

RESULTS

Calibration and Validation

The average calibration accuracy for the disease control group was 0.44° with a standard deviation (SD) of $\pm 0.91^\circ$ and coefficient of variation (CV) of 2.05. The median calibration accuracy was 0.19° . The delirium patients had an average calibration accuracy of 0.97° (SD= $\pm 0.65^\circ$, CV=0.67) and median calibration accuracy of 0.96° . The average validation accuracies for the disease control group and delirium group were 0.88° (SD= $\pm 0.51^\circ$, CV= 0.58) and 1.14° (SD= $\pm 0.44^\circ$, CV= 0.38) respectively. The median validation accuracy for the disease control and delirium group were 0.68° and 1.14° . Table 3 reports the calibration accuracy and validation accuracy for each participant in the disease control group and Table 4 shows the same metrics for each participant in the delirium group.

Saccadic Latency in Horizontal Gap Overlap Saccade

Figure 3 presents the mean latency for both saccade trials for the disease control and delirium group. The mean latency of the gap saccades was 441.28 (SD= ± 308.17 ; CV= 0.70) milliseconds and the mean latency of overlap saccades was 505.57 (SD = ± 303.83 ; CV=0.60) milliseconds in the disease control group. The median latencies of the gap and overlap saccades were 336 and 443.27 milliseconds. For the delirium group, the mean gap saccade latency was 649 (SD= ± 284.08 ; CV=0.44) milliseconds and the

mean overlap saccade latency was 579.88 (SD= \pm 351.80, CV=0.61) milliseconds. The median gap and overlap saccadic latencies were 635.64 and 519.88 milliseconds for the delirium group. Tables 5 and 6 report the mean and median latencies of the 12 trials for the gap and overlap saccades, standard deviations, and coefficient of variation for all participants in the disease control group. The mean and median latencies of the 12 trials for the gap and overlap saccades, standard deviations, and coefficient of variation for all participants in the delirium group are also shown in Tables 7 and 8.

Table 3. Calibration and Validation Accuracy in Degrees in Disease Control Group.

Subject	CAM-S score	Calibration accuracy (°)	Validation accuracy (°)
1	0	3.85	1.25
2	1	0.15	0.69
3	1	0.12	0.58
4	0	0.16	0.46
5	3	0.19	0.45
6	3	0.36	1.63
7	2	0.18	0.66
8	0	0.27	0.49
9	2	0.16	0.47
10	1	0.08	0.5
11	2	0.17	0.3
12	2	0.19	1.96
13	0	0.21	0.96
14	1	0.27	1.39
15	4	0.36	0.82
16	3	0.39	1.51

Table 4. Calibration and Validation Accuracy in Degrees in Delirium Group.

Subject ID	CAM-S score	Calibration accuracy (°)	Validation accuracy (°)
17	8	1.63	0.71
18	10	0.33	1.58
19	11	0.96	1.14
20	4	-	-

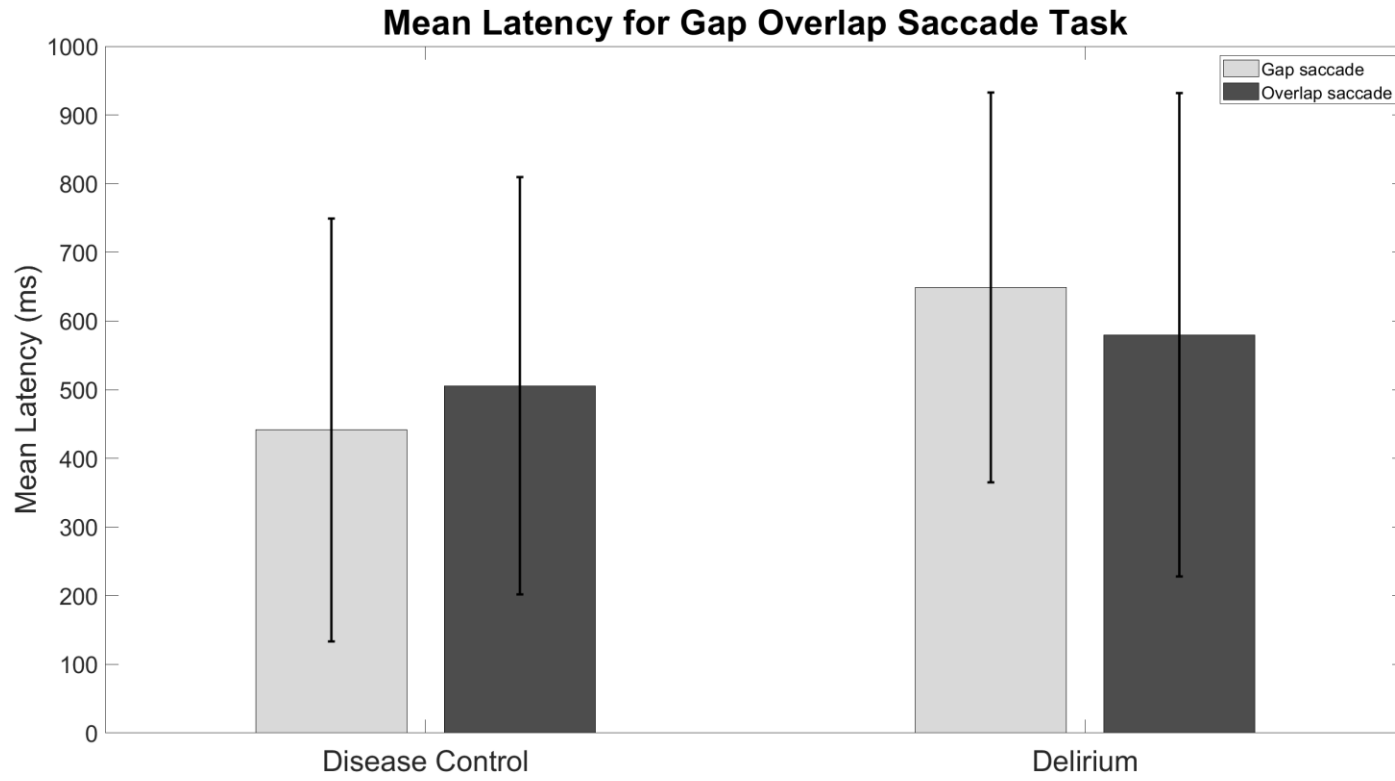


Figure 3. Mean Latency for Gap Overlap Saccade Task. The error bars represent the standard deviation for each type of saccade trial.

Table 5. Mean and Median Latencies for Gap Saccade and Their Standard Deviations and Coefficient of Variation for the Disease Control Group. *– indicates no data.

Subject	CAM-S score	Gap mean	Gap median	Gap STD	Gap CV
1	0	589.0016	588.559	70.71837774	0.120064831
2	1	586.0462857	458.978	426.512809	0.727780074
3	1	356.768	294.789	163.9091694	0.45942789
4	0	287.677	262.555	128.5878436	0.446986876
5	3	797.6069	671.6315	290.798508	0.364588757
6	3	591.029	426.275	374.7111768	0.633997954
7	2	_*	_*	_*	_*
8	0	296.148	255.7985	130.8239387	0.44175189
9	2	321.5925	276.7745	259.9002042	0.808166248
10	1	451.3107273	480.368	129.5891419	0.287139512
11	2	509.3189091	315.744	419.1861219	0.82303271
12	2	591.1728	525.279	292.1322634	0.494157146
13	0	286.5834167	309.8405	86.30443203	0.301149428
14	1	395.16	299.6885	320.1293292	0.810125846
15	4	496.4431667	270.846	502.3813065	1.011961369
16	3	334.1354444	194.806	388.0712492	1.161418986

Table 6. Mean and Median Latencies for Overlap Saccade and Their Standard Deviations and Coefficient of Variation for the Disease Control Group.

.Subject	CAM-S score	Overlap mean	Overlap STD	Overlap CV
1	0	863.381	544.9975949	0.631236493
2	1	529.659875	157.2586585	0.296904987
3	1	536.0438182	101.3201433	0.189014666
4	0	786.12725	621.9065091	0.791101579
5	3	745.6058	158.3907866	0.212432342
6	3	268.20325	182.4405313	0.680232366
7	2	386.644	0	0
8	0	281.9016	168.9553235	0.599341485
9	2	360.2563333	231.992657	0.64396552
10	1	469.1973636	140.7901601	0.300065966
11	2	502.2746	180.1199733	0.358608564
12	2	503.8232	251.7349419	0.499649365
13	0	379.9121667	114.8811619	0.302388741
14	1	652.6390909	454.729502	0.696754927
15	4	349.58	198.5845189	0.568066019
16	3	444.439	146.2476391	0.329061219

Table 7. Mean and Median Latencies for Gap Saccade and Their Standard Deviations and Coefficient of Variation for the Delirium Group. *– indicates no data.

Subject	CAM-S score	Gap mean	Gap median	Gap STD	Gap CV
17	8	670.9427778	687.469	292.3110662	0.435672126
18	10	636.9415	636.9415	339.4628738	0.532957695
19	11	624.2284286	533.784	306.6594863	0.491261648
20	4	–*	–*	–*	–*

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Table 8. Mean and Median Latencies for Overlap Saccade and Their Standard Deviations and Coefficient of Variation for the Delirium Group. *– indicates no data.

Subject	CAM-S score	Overlap mean	Overlap median	Overlap STD	Overlap CV
17	8	704.0198333	519.7465	423.264358	0.601210844
18	10	552.872	552.872	0	0
19	11	500.1156667	477.824	318.2474986	0.636347789
20	4	–*	–*	–*	–*

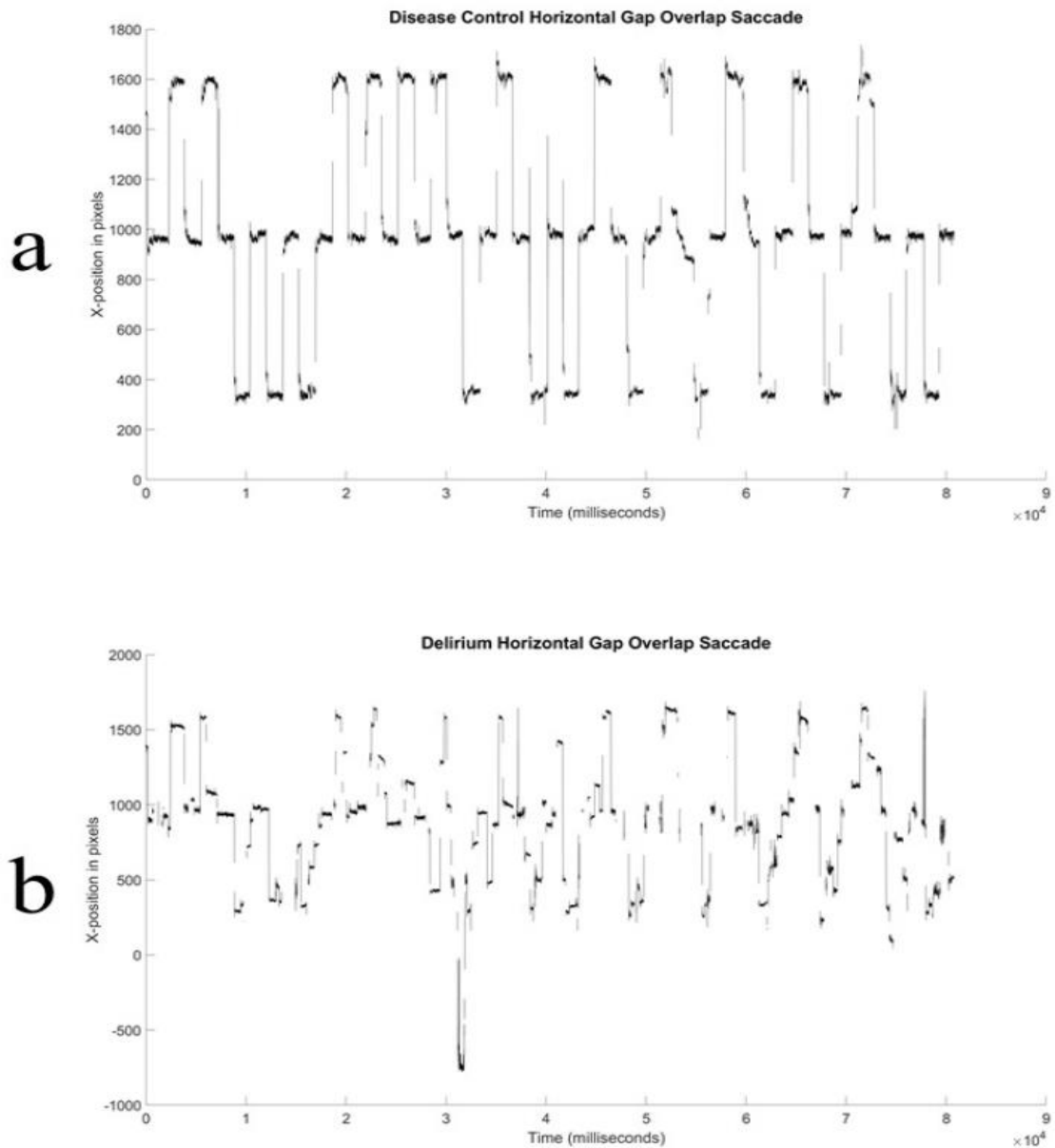


Figure 4. Gap Overlap Saccade X-Coordinate Position of Gaze Over Time. a) The x-coordinate position over time of Subject 13 in the disease control group with a CAM-S score of 0. b) The x-coordinate position over time of Subject 19 in the delirium group with a CAM-S score of 11.

Total Target Gaze Duration in Smooth Pursuit

Tables 9 and 10 report the total duration of gaze on the horizontal and circular smooth pursuit target in the disease control and delirium patients. The average gaze duration for the horizontal smooth pursuit target in the disease control and delirium groups were 8.09 (SD= ± 6.34 , CV= 0.78) and 4.11 seconds (SD= ± 5.83 , CV= 1.42). The median gaze duration for the horizontal smooth pursuit target for the disease control and delirium groups were 9.43 and 1.91 seconds respectively. The average gaze duration for the circular smooth pursuit target in the disease control and delirium groups were 6.67 (SD= ± 4.78 , CV= 0.72) and 4.05 seconds (SD= ± 3.27 , CV=0.81). The median gaze duration for the circular smooth pursuit target for the disease control and delirium groups were 7.75 and 4.51 seconds. Figure 6 shows the x-position of the gaze over time of one subject from each group for the horizontal smooth pursuit task. Figure 7 demonstrates the x-position of the gaze over time and X, Y- coordinates of one subject from each group for the circular smooth pursuit task.

Table 9. Total Gaze Duration on Smooth Pursuit Targets in Disease Control

Patients.

Subject	CAM-S score	Horizontal Smooth Pursuit Duration (ms)	Circular Smooth Pursuit Duration (ms)
1	0	0	0
2	1	11372	7485
3	1	17040	16268
4	0	504	3335
5	3	11743	8008
6	3	7154	607
7	2	185	5603
8	0	12754	9557
9	2	8945	11403
10	1	12791	11562
11	2	11466	8074
12	2	1877	1188
13	0	19852	9663
14	1	9905	2965
15	4	1654	845
16	3	2244	10131

Table 10. Total Target Gaze Duration on Smooth Pursuit Targets in Delirium

Patients.

Subject	CAM-S score	Horizontal Smooth Pursuit Duration (ms)	Circular Smooth Pursuit Duration (ms)
17	8	578	7189
18	10	3233	2871
19	11	12605	6156
20	4	23	0

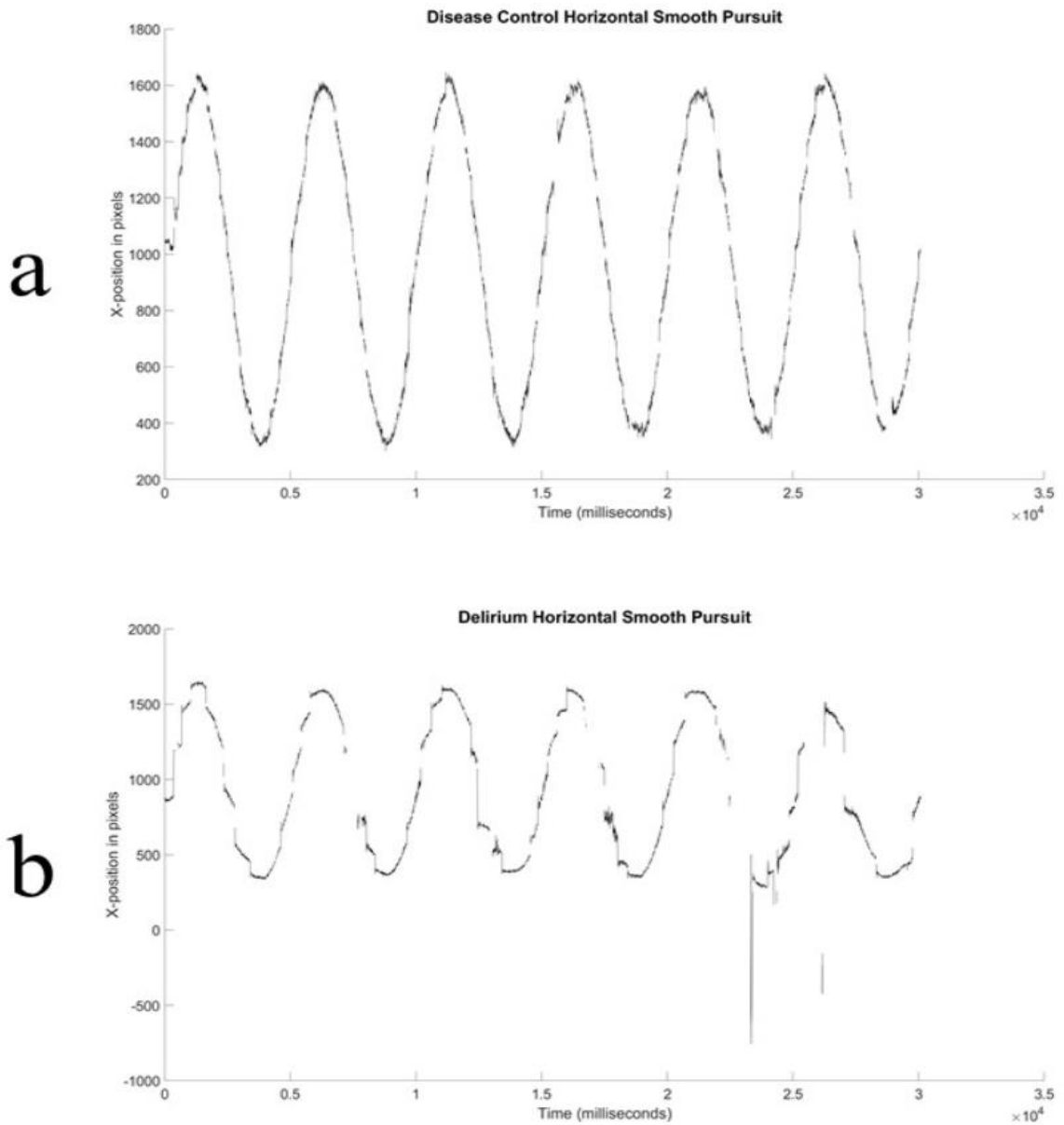


Figure 5. Horizontal Smooth Pursuit X-Coordinate Gaze Position Over Time. a) The x-coordinate position over time of Subject 13 in the disease control group with a CAM-S score of 0. b) The x-coordinate position over time of Subject 19 in the delirium group with a CAM-S score of 11.

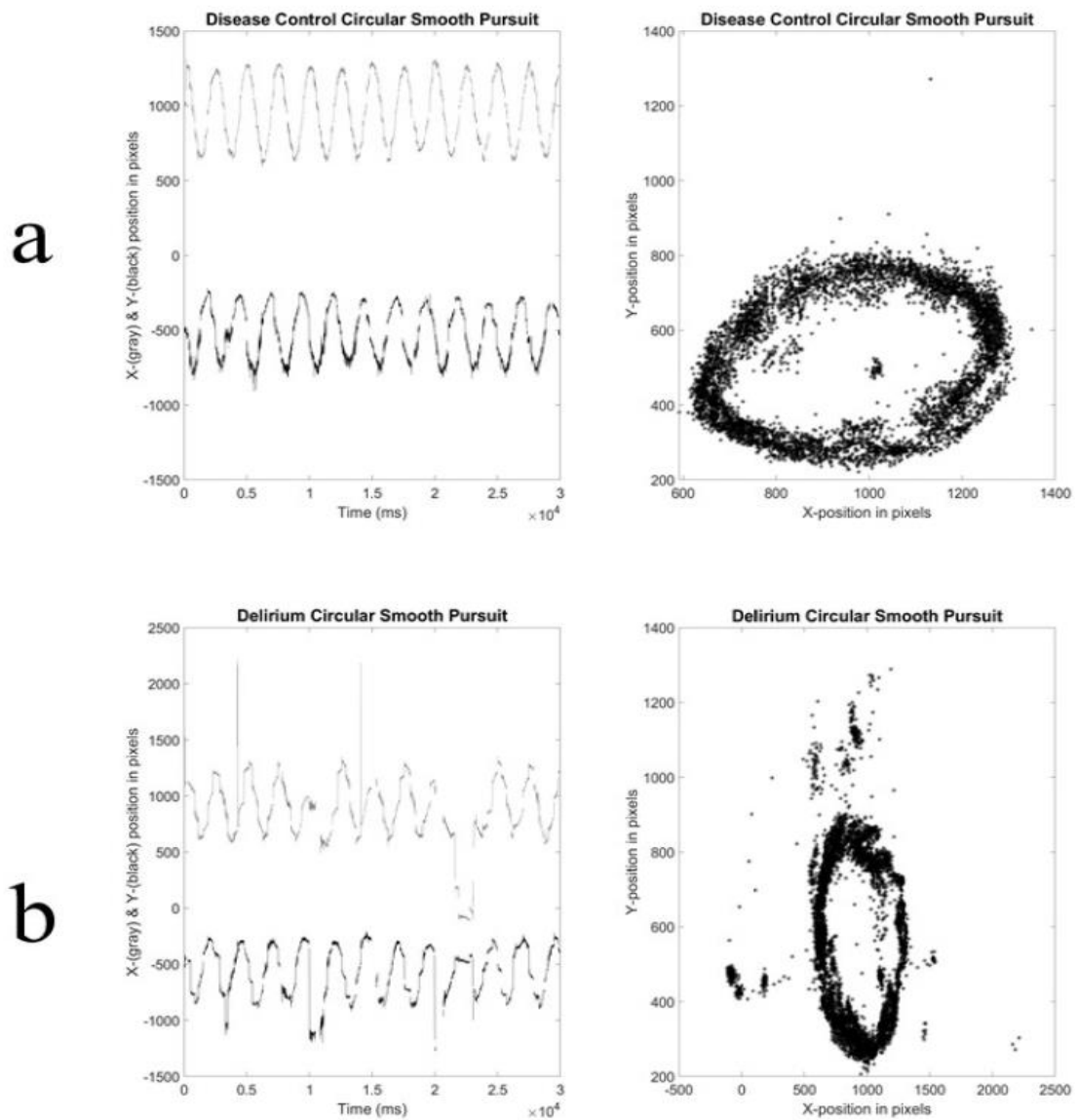


Figure 6. Circular Smooth Pursuit X-Coordinate Gaze Position Over Time and X, Y-Coordinates. a) The x-coordinate position over time and X, Y-coordinates of Subject 13 in the disease control group with a CAM-S score of 0. b) The x-coordinate position over time and the X, Y-coordinates of Subject 19 in the delirium group with a CAM-S score of 11.

DISCUSSION

The study of eye movements in delirious patients is poorly understood in the research community, therefore, the present study seeks to assess the feasibility in utilizing eye-tracking methods to detect delirium. We have used gap and overlap saccade and smooth pursuit paradigms in our experimental procedure and examined the calibration and validation data, saccadic latencies, and total gaze duration on the smooth pursuit target in the eye gaze data.

Horizontal Gap Overlap Saccades

Figure 4 shows Subject 13 and 19's x- position in gaze over time for the horizontal gap overlap saccade task. Here, we see some differences in gaze between Subject 13 in the disease control group with a CAM-S score of 0 and Subject 19 in the delirium group with a CAM-S score of 11. Subject 19 has more missing data points on the plot and may suggest inattentiveness or poor tracking. It also appears that Subject 19 is making multiple short saccades along the way to the target saccade destination. These multiple short saccades suggest dysmetria, or the impaired performance in accurate movements (Manto, 2009). More specifically, this is an example of hypometria where the subject demonstrated undershoot in reaching the target saccade, resulting in short saccades to compensate for the undershoot.

Previous studies have demonstrated that reduced brain volume in the cerebellum, thalamus, and frontal lobes are associated with visual attention impairment in delirious patients who were discharged from the ICU (Gunther, et al, 2012). Cavallari et al. (2016) found patients with abnormalities of the corpus callosum, thalamus, and cerebellum to have increased incidence and severity of delirium. This study also found that abnormalities of the cerebellum was most significantly associated with postsurgical delirium. According to Schmahmann (2004), the universal cerebellar impairment is dysmetria which includes dysmetria in eye movements. This type of dysmetria is referring to the inability to control eye movements, thus resulting in inaccurate saccades. The cerebellum plays a vital role in managing the accuracy of saccades and does so by providing the drive towards the target, tracking the target, and ending the saccade by eliminating the drive (Leigh and Zee, 2006; Quaia, Lefèvre, & Optican, 1999). In addition, lesions on the cerebellum may result in permanent damage towards the maintenance of saccades (Optican & Robinson, 1980). These lesions would not abolish an individual's oculomotor function, but would rather slow it down and making them more variable and imprecise (Robinson & Fuchs, 2001). Therefore, possible cerebellar damage in our subjects with delirium may explain the catchup saccades to compensate for the undershoot.

Saccadic Latency

Our calculated means and medians for the gap and overlap saccadic latency for the delirium group appear to be longer than that of the disease control group. This is consistent with previous studies that have demonstrated longer latencies in the disease group (Crawford, et al., 2013; Yang, Wang, Su, Xiao, & Kapoula, 2013). However, based on the standard deviation error bars in Figure 3, there is some overlap in saccadic latencies between the two groups which may be attributable to poor calibration and validation.

Smooth Pursuit

Similar to Figure 4, we notice some differences in gaze between Subject 13 and 19 in Figure 5, which shows the x-coordinate position over time for the horizontal smooth pursuit task. We notice that Subject 13's gaze appears more continuous and smooth than that of Subject 19's. From Figure 5b, we see that Subject 19 seems to follow the path of the horizontal smooth pursuit but her gaze appears more jagged than that of Subject 13's. In the circular smooth pursuit task, we notice some differences in eye movements between Subjects 13 and 19 as well (Figure 6). Similar to the horizontal smooth pursuit data, Subject 19's the circular smooth pursuit gaze data suggest more irregular movements than Subject 13's, who's gaze appears more smooth and continuous. In Figure 6b, right plot shows Subject 19's gaze in X,Y coordinates and we notice more data points located further out of the circular trajectory than that of Subject 13's. As previously mentioned, possible cerebellar dysfunction may account for patients' impaired

oculomotor function, resulting in the variable and imprecise eye movements we are witnessing in Subject 19's eye gaze for the horizontal and circular smooth pursuit tasks.

Total Gaze Duration on Target

The mean and median total gaze duration on the horizontal and circular smooth pursuit targets in the disease control group are longer than that in the delirium group. We captured the duration our patients maintained their gaze on the target; longer gaze duration on the target suggests longer sustained attention. These metric results are consistent with our belief that the disease control subjects would have longer sustained attention or longer gaze duration throughout the smooth pursuit tasks. However, like the saccadic latencies, there is some overlap in the gaze duration between the two groups that may also be attributable to poor calibration and validation.

Calibration and Validation Accuracy

In addition to the cerebellar damage that may have occurred in some of our patients, the calibration and validation may have contributed to the highly variable eye gaze data. According to Tables 3 and 4, the calibration and validation accuracies for Subject 13 are 0.21° and 0.96° and for Subject 19 are 0.96° and 1.14° respectively, indicating that Subject 19 has poorer calibration and validation. The calibration and validation accuracy values suggest how far away the eye gaze is from the real visual stimuli in degrees; therefore, the greater the value, the lower the accuracy. We notice

high variation in the calibration accuracy in disease control patients with a CV of 2.05 and the delirium group's calibration accuracy had a coefficient of variation of 0.67. This may be due to the highly variable conditions that the patients are being treated for at MGH. According to Tobii Pro (n.d.), factors that can result in problematic eye-tracking include glasses with more than one power, eye surgery, and other ocular abnormalities. Some of our patient participants have ocular conditions and had ocular surgery in the past, which greatly affects eye tracking. These conditions and surgeries include cataract surgery, strabismus surgery, and occlusion in the eye, leading to partial blindness. Eye-trackers work by calculating a vector formed by the angle between the cornea and pupil reflection and ultimately using this vector to calculate the gaze direction (Tobii Pro, n.d.). The cataract and strabismus surgeries our participants had may leave scar tissue on the cornea which affects the eye-tracker's ability to capture the corneal reflection, resulting in poor calibration.

Limitations

Recruitment of patients from the inpatient units and ICU is challenging for the patients who are receiving intensive level of care. Throughout the course of treatment, hospitalized patients may often feel exhausted, sleep-deprived and confused due to the treatments they receive and disruptions from loud medical equipment and hospital staff. These factors along with the recruitment restraints due to the COVID-19 pandemic contributed to the low sample size we recruited in the given time frame. Another

limitation is the setting of study sessions. The study sessions took place in hospital rooms in the ICU or inpatient unit at MGH and there were distractions coming from the hallways, medical equipment, and patients in the adjacent bed. These noises may have some part in distracting our subjects, affecting their ability to fully attend to the oculomotor tasks asked of them.

Implications for Future Research

In this study, we closely examined calibration and validation data, saccade latencies, and total gaze duration on the smooth pursuit target in disease control and delirious participants. Additional research is needed to further assess the feasibility of using eye-tracking to capture delirium features. One of the biggest challenges our study faced was recruitment in the inpatient setting where patients are often tired and unwell, which affected patient's ability and motivation to complete the tasks to the absolute best of their abilities. In addition, our participants were diagnosed with a variety of medical conditions that may affect their ability to complete the oculomotor tasks or affect the eye-tracker's ability to calibrate. In a future study, scientists may replicate this experimental design and recruit for healthy controls with no pre-existing conditions that may impact their cognitive or oculomotor functioning instead of disease controls. Through this method, scientists may find more accurate eye-tracking calibration and validation data. Despite having positive CAM-S assessments, four of the eight participants in the delirium group with a CAM-S score range of 4-11 have successfully completed the oculomotor

tasks. On the other hand, the four participants with a higher degree of severity in delirium (CAM-S score range of 8-14) were unable to follow the visual stimuli. This information may be helpful for researchers who are interested in replicating this experimental design in patients with milder delirium who are more likely to understand that task instructions and complete the oculomotor battery. Researchers may also investigate the correlation between the eye-tracking metrics and CAM-S scores. This would provide useful information about the level of severity of delirium features captured by eye-tracking.

The present study recruited participants from MGH with a wide variety of diagnoses and conditions. Many of our participants presented to the hospital for headaches, seizures, and altered mental status and were admitted for further evaluation via EEG recordings. With delirium being multifactorial and complex, accurate assessment of the condition is challenging. Previous studies have shown that eye-tracking has been an effective assessment for attention and have demonstrated great promise as an assessment for diseases such as Alzheimer's disease (Crawford, et al., 2013; Peltsch, Hemraj, Garcia, & Munoz, 2014; Yang, Wang, Su, Xiao, & Kapoula, 2013). Due to concerns about the quality of eye-tracking calibration, we believe the eye-tracking metrics data may have some degree of inaccuracy. Nevertheless, we were able to capture and visualize the path of our subjects' eye movements as they followed the visual stimuli. Through these visualizations, we observed some differences in gaze between Subject 13 in the disease control group and Subject 19 in the delirium group. These results may

provide valuable information for the future research that will ultimately develop tools to detect delirium.

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CURRICULUM VITAE

