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Diagnosis of myasthenia gravis using fuzzy gaze tracking software

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Summary

Myasthenia Gravis (MG) is an autoimmune disorder, which may lead to paralysis and even death if not treated on time. One of its primary symptoms is severe muscular weakness, initially arising in the eye muscles. Testing the mobility of the eyeball can help in early detection of MG. In this study, software was designed to analyze the ability of the eye muscles to focus in various directions, thus estimating the MG risk. Progressive weakness in gazing at the directions prompted by the software can reveal abnormal fatigue of the eye muscles, which is an alert sign for MG. To assess the user's ability to keep gazing at a specified direction, a fuzzy algorithm was applied to images of the user's eyes to determine the position of the iris in relation to the sclera. The results of the tests performed on 18 healthy volunteers and 18 volunteers in early stages of MG confirmed the validity of the suggested software.

Introduction

Myasthenia Gravis (MG) is an autoimmune disorder in which the body immunity system attacks its own tissues [1]. The main symptom of this disease is progressive muscle weakness, which leads to premature fatigue during daily activities, and even respiratory paralysis or death in severe cases [2]. MG can occur at any age; however, it is more common among women aged 20 to 40, and men who are over 70 years old. Current literature reports an incidence rate of 14 cases per 100000 individuals, and a prevalence in women [3]. The cause of MG is still unknown; in some cases, it may present together with other autoimmune disorders and in rare cases, it can be caused by Thymus tumors.

Based on the organs involved, the symptoms of MG can range from mild to severe. Myasthenia Gravis usually affects the muscles around the eyes, mouth, throat, and limb terminals, and causes fatigue and ongoing weakness while using them, thus causing the patient's ability to cope with normal physical activities to become gradu-

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ally reduced and limited. Muscle weakness gets worse when working hard, ameliorating with rest, and can arise or disappear intermittently.

Myasthenia Gravis can affect all the muscles and/or organs that have conscious movements. The first symptoms of MG arise in eye muscles, with premature fatigue and eyelid drooping. Gradually, further symptoms can be observed in feet and arms (inability to perform daily activities), face, throat, and neck (problems in speaking, chewing and swallowing), and respiratory muscles. These symptoms can improve seemingly randomly and resume later on.

Misdiagnosis or ignoring MG can lead to respiratory problems and eventually death [2]. The first step to diagnose MG is to check up the body and nervous system. Most patients experience severe fatigue while speaking, to the extent that their voice cannot be heard afterwards. Moreover, after eating a few morsels, the patient's jaw becomes fatigued. In severe cases, the patients may need to use their hands to hold their jaw closed while sitting. In addition, intermittent diplopia while studying or watching TV, and muscular contraction during a long-term manual activity are common symptoms. Therefore, in order to diagnose MG, the physician requests the patient to speak a few words, count numbers, or gaze at something for a specific amount of time. Premature fatigue or inability to perform such activities are symptoms of Myasthenia Gravis. Eye movement disorders or eye muscle weakness are also important warning signs.

If Myasthenia Gravis is suspected, appropriate diagnostic tests should be carried out [4]. The most common one is the Tensilon test [5], in which Edrophonium chloride is injected to the patient to prevent the destruction of acetylcholine, and temporarily restore muscle strength. Positive response to this medicine confirms the MG diagnosis. However, this test may cause some complications due to its cholinergic side effects [6]. Furthermore, toxicity associated with the Tensilon test has been reported [7].

Other diagnostic tests include *Nerve Stimulation Test* (analysis of the ability of the nerves to send signals to muscle/organ during continuous stimulation), *EMG Test* (measurement of the electric activity between brain and muscle by inserting a fine electrode into the muscle, which is usually painful), *Blood Test* (to check for the destructive antibodies of acetylcholine receptors in blood), *Computed Tomography* or *CT scan* (detection of an abnormal Thymus gland or tumor in the Thymus), and *Pulmonary Function Test* (measuring the breathing strength).

Finding a safe, non-invasive, and inexpensive alternative for the Tensilon test has been of interest for many years [7]. For example, Odel and colleagues [6] suggested to measure the mobility of the muscles during a short period after wake-up to diagnose MG. In another study [8], the opening between the eyelids was measured before and instantly after a 2-minute application of ice to a ptotic eyelid. The results of the ice test and rest test were compared in a further article [9].

The eye muscles are more active and sensitive compared to other muscles [10]. Therefore, primary symptoms of various disorders, e.g. brain tumors and MS, become immediately obvious in the eye [11]. This is also the case of MG, whose early symptoms arise in eye muscles, with severe and premature fatigue, as well as drooping eyelids [1]. Other symptoms include diplopia and inability to keep the eyes fixed for long periods, specifically known as Ocular Myasthenia [12]. Hence, the user's ability to move his/her eyeballs can be used as a criterion to estimate the risk of MG.

In this study, software was designed to measure the user's ability to focus and keep gazing at various directions for specific periods. This procedure engages the exterior eye muscles, and will result in early eye fatigue in individuals with Myasthenia Gravis. The performance of the subject is evaluated using a fuzzy computer vision algorithm. By rating the subject's ability to follow software commands to focus in eight main directions, the risk of MG can be estimated.

Determining the position of the eye in the face and exact gaze tracking has attracted much attention in recent years.

Some applications involve visual computer interfacing [13], psychological research [14], evaluation of athletes' visual performance [15], marketing and advertising [16], and medical diagnostics [17, 18]. Several algorithms have been suggested for eye tracking [19]. In the method presented here, iris location is detected using a fuzzy algorithm, and gaze direction is determined by the combined use of the fuzzy data of both eyes. The results obtained confirm the accuracy of the software in diagnosing MG.

Methodology

In the Myasthenia Gravis anomaly, nerve-to-muscle connections are destroyed by antibodies. Hence, the activities of acetylcholine receptors that transfer messages from nerves to muscles are disrupted. A decrease in the number of active receptors leads to fewer muscle fibers being involved in contraction, which in turn leads to evident muscle weakness. As previously shown [10], eye muscles are sensitive and active, thus being subjected to attenuator anomalies like MG. Therefore, we decided to use this characteristic to estimate the risk of MG by measuring the mobility of the patients' eyeballs.

Eye Muscles Anatomy

Eyeball motion is controlled by six extraocular muscles, comprising two rectus and four oblique muscles [20]. The rectus muscles originate at the surrounding ring of the optic nerve (Annulus of Zinn), and are connected to the front half of the eyeball (anterior to its equator) from four directions: lateral, medial, superior, and inferior. The oblique muscles contain the superior and inferior muscles; the superior muscles are the longest and thinnest extraocular muscles that originate at the back of the orbit, and connect under the superior rectus to the posterior portion of the eye's equator. The inferior oblique muscles originate at the lower front of the nasal orbital wall, pass under the inferior rectus and are connected to the posterior portion of the eye's equator. Figure 1 shows the position of these muscles from different angles.

Each of these muscles pulls the eye towards a specific direction. The lateral rectus muscles and the inferior ones pull the eye outward and forward, respectively. The superior and inferior oblique muscles help to stabilize eye movements and are responsible for the rotation of the eye axis. According to Hering’s law [21], in order to move both eyes in the same direction, both of the corresponding muscles should receive the same neural signals. Paired extraocular muscles that work synergistically to direct the gaze in a given direction are called *Yoke Muscles*. Some examples include the lateral rectus of the right eye and the medial rectus of the left eye when gazing right (and vice versa), the superior rectus of the right eye and the inferior oblique of the left eye when gazing up-right (and vice versa), and the inferior rectus of the right eye and the superior oblique of the left eye when gazing down-right (and vice versa).

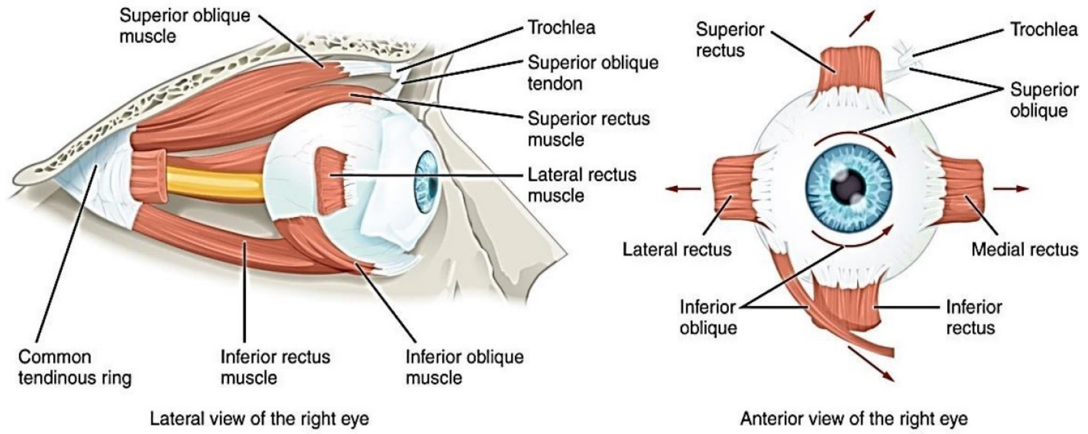


Figure 1) The structure of the extraocular muscles [20]

Figure 2 shows the yoke muscles in different eye movements. In this figure:

- R is the abbreviation of Right in the beginning of the symbol and in the end, it is representative of Rectus.
- L is representative of Left in the beginning of the abbreviation, and in the middle, it stands for Lateral.
- M, I, and S stand for Medial, Inferior, and Superior, respectively.

Figure 2 shows that gazing up-right, up-straight, up-left, down-right, down-straight, and down-left implies the engagement of all six extraocular muscles, and reveals the muscle strength/ weakness efficiently. In the designed software described below, these motions will be considered.

Fuzzy Gaze Detection Software

In this study, software was designed to measure the speed and stability of the user's eyes in tracking and concentrating in different directions, using a fuzzy gaze detection algorithm. The descending trend of this speed in continuous enforcement of eye muscles can be a symptom of Myasthenia Gravis. The motions used for testing engage all six extraocular muscles, thus accelerating fatigue. The details of the software algorithm and implementation are explained below.

Fixation of the Eye Images

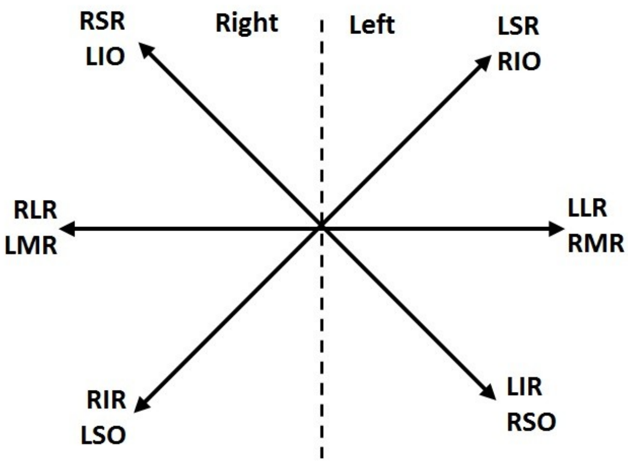
In order to assess how accurately the user can track the directions prompted by the software, gaze direction should be determined by a camera along with a computer vision algorithm. Various methods have been suggested for gaze detection in recent years [23].

One of the challenges associated with automatic gaze detection is the changes of the subjects' face/eye location in front of the camera. In this study, we used a technique similar to the one suggested in a previous study [13]. In this method, the user's eyes position must be fixated in front of a high-resolution camera, so that the software can mainly focus on the user's gaze direction, instead of finding the position of the eyes (usually erroneous and time consuming). To achieve an ideal position, a short rod with a soft sponge on top is used, as shown in Figure 3.a. The user adjusts the height of the rod, as well as the distance between his/her face and the camera, and then puts his/her chin on the rod, gazing at the camera motionless, as depicted in Figure 3.b. After running the software and selecting the calibration choice, a page like the one shown in Figure 3.c. appears. The user's eyes must be completely inside the red frame during the software operation. Otherwise, the procedure will restart.

Fuzzy Gaze Detection

When the eyes are fixated inside the frame, an image of the face is captured with the high resolution camera and cropped so that the image of the eyes remains. As per Figure 4, the image of each eye is divided into six areas.

To detect the gaze direction, the sug-



RSR and LIO	Eyes up and right
LSR and RIO	Eyes up and left
RLR and LMR	Eyes right
LLR and RMR	Eyes left
RIR and LSO	Eyes down and right
LIR and RSO	Eyes down and left

Figure 2) The yoke muscles of the eye [22]

gested algorithm uses the ratio of non-white pixels of the eye image (for example iris or pupil) to the white pixels (sclera). The V parameter in HSV color space is used to detect the sclera [24]. At first, a Gaussian smoothing filter is applied on the eye image to eliminate redundant details like eyelashes, iris holes, and blood vessels in the sclera. Then, a binary image is created from the V plate of the image, using a threshold about 70% of the maximum brightness of the image. This threshold depends on the light conditions and is automatically adjusted in the calibration step. The white pixels of the binary image mostly show the sclera, while the black pixels represent other parts of the eye. The ratio of the black pixels to the white ones is calculated in each area and constitutes the E set according to equation 1:

$$E = \left\{\mu_i = \frac{\text{number of black pixels in area } i}{\text{number of white pixels in area } i} \mid 1 \leq i \leq 12\right\} \quad \textbf{Eq. 1}$$

Now, the relation between the E members and gaze direction should be determined. As illustrated in Figure 4, μ_i values show the white part(s) of the eye, which correspond to the direction of the gaze. For instance, if the lower parts of the eyes are more white (μ_i values for i = 4, 5, 6, 10, 11, and 12 are low), it can be concluded that the user is gazing upward. However, the overall conclusion is not that simple and straightforward. For example, the effect of the upper curved line of the eyes in areas 1, 2, 3, 7, 8, and 9, which affects the corresponding μ_i values, must be considered. This is also the case when the eyelids cover the upper area of the eyes while looking down. Moreover, the μ_i values are not consistent when gazing at different directions. In these cases, discrepancies in the μ_i values may arise and cause problems with making distinct decisions based on their crisp values. Thus, utilizing a fuzzy classifier that uses the E values to determine the gaze direction seems sensible.

Using fuzzy functions and sets to solve imprecise problems has played an important role in classification literature for many years. Specifically, the Mamdani fuzzy systems are known as simple and effective solutions in such cases [25]. In this scheme, the imprecise inputs are assigned to fuzzy sets using membership functions. Having a fuzzy rule base, com-

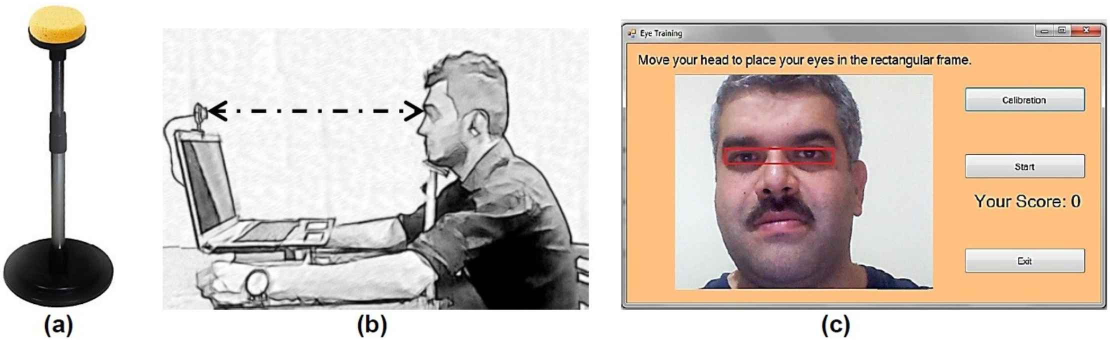


Figure 3. a) Rod to keep the head fixed, b) Fixation of the eye images, c) Software calibration page

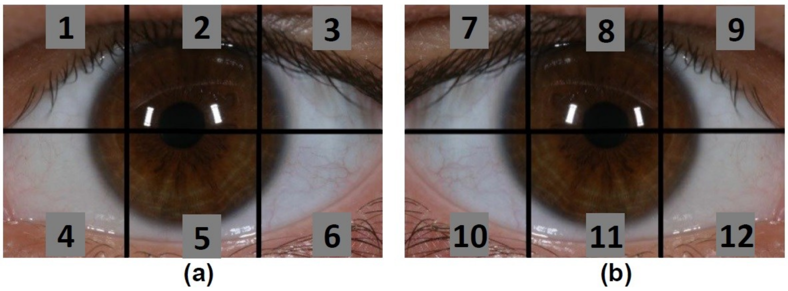


Figure 4) Numbering the areas of a) left eye and b) right eye (frontal view)

prising IF-THEN rules suggested by an expert, the output fuzzy sets are stimulated. Ultimately, a distinct response for the problem is determined by a defuzzifier block. Figure 5 depicts the fuzzy problem solving process.

In our study, the values of the E set were fuzzified and used to determine the gaze direction (angle). Three input fuzzy sets, L, M, and H, were defined, indicative of being *white*, *partially white*, and *non-white*, respectively. Common triangular membership functions were applied for fuzzification step [27], as illustrated in Figure 6.

We consider eight gaze directions, as shown in Figure 7. Continuous turning of the eyes towards the requested directions causes tension and fatigue on the extraocular muscles, which is intensified in the presence of MG.

Regarding Figure 7, eight output classes were defined, as shown in Figure 8.a. Relevant defuzzifier functions are illustrated in Figure 8.b. The horizontal axis is the gaze angle in the polar coordinate system, ranging from 0° (gazing right) to 315° (gazing down-right). Mamdani minimum function and Center-Of-Gravity combination scheme was used for the defuzzification step [25]. Note that the DR and R classes are adjacent in the circular view (Figure 8.a), while this is not the case in Figure 8.b. Hence, if both of

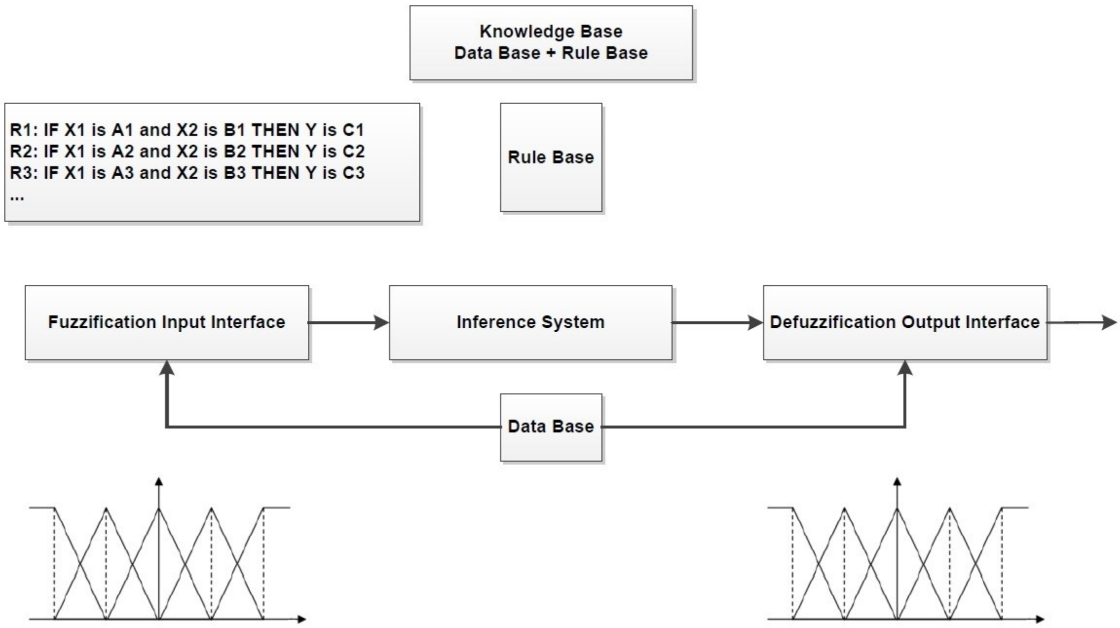


Figure 5) Fuzzy problem solving process [26]

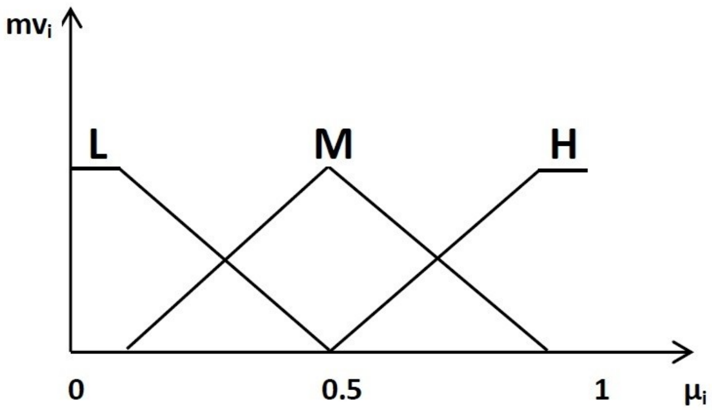


Figure 6) Fuzzifier functions (mv: Membership Value)

them were triggered in the defuzzification step, the horizontal axis in Figure 8.b was considered circular to calculate the Center-Of-Gravity.

According to the classes in Figure 8, there are eight rules in the fuzzy rule base. Table 1 depicts these rules based on AND combination. Note that on the lower row of Figure 7-looking down-, eyes were kept open by an instrument. In the real world, the eyelids cover half of the eyes while looking down, and the upper half of the eyeballs cannot be seen. As a result, in downward gazing rules, all the inputs corresponding to upper halves of the eyes were considered to be H in Table 1.

Another characteristic of the above fuzzy rules is simultaneously considering the images of both eyes. This makes the algorithm more reliable even when luminance changes, noise, facial features, and changes in imaging angle are encountered. In Table 1 and Figure 4, we observe that mv_4 and mv_6 are not necessarily consistent with mv_{10} and mv_{12}, respectively, due to the exterior structure of the eye.

Analyzing the above algorithm on the Columbia Gaze database [13] showed over 80% efficiency and adequate speed, and thus the software was deemed ready to capture the image of the eyes and detect the gaze direction, if the fixation conditions are satisfied.

Software Strategy

After the initial calibration of the software, the user fixates his/her eyes in front of the camera. Then, the software vocally requests the users to gaze at a specific direction without moving their head and face (only by moving the eyeball). The user must keep gazing at the specified direction for 10 seconds. The duration of accurate gazing is determined and recorded by the software as the user's score. Then, the user should rest for 5 seconds by closing his/her eyes. This process is repeated for 15 times at various random directions, for a total duration of less than 5 minutes. After 10

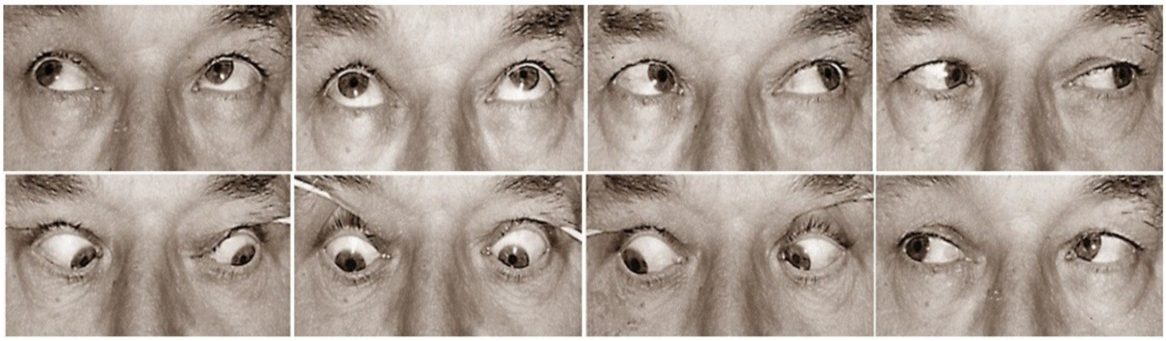


Figure 7) Eight gaze directions [22]

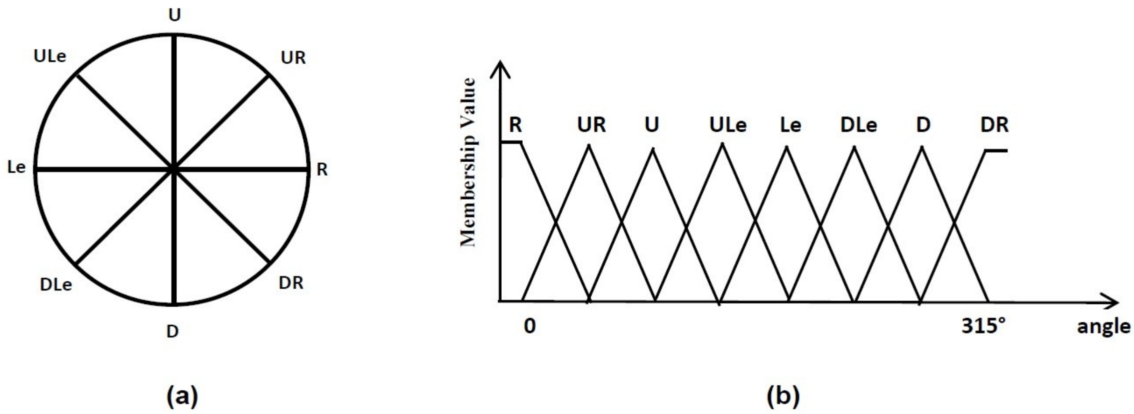


Figure 8. a) Angular gaze directions from frontal view b) Defuzzifier functions (U: Up, D: Down, Le: Left, R: Right)

minutes rest, the process is repeated and the scores of these two rounds are averaged. The users are asked to close their eyes when feeling fatigue or pain in their forehead.

Results

In order to test the efficiency of this software to diagnose Myasthenia Gravis, we asked 18 healthy volunteers and 18 volunteers with MG, confirmed by the Tensilon test performed within the past two months, to use the software in one session. The comparative chart in Figure 9 shows the average scores of these two groups. The horizontal axis is the number of vocal commands issued by the software.

Discussion and Conclusions

As is evident in Figure 9, the average scores of the MG patients decline over time, while the performance of the healthy volunteers is consistent throughout the test. This confirms the ability of the proposed software to help physicians to diagnose MG, even at early stages, which is of vital importance in the treatment process. This test can be considered as a non-invasive and safe alternative to other diagnostic methods for MG. The average scores and relevant stan-

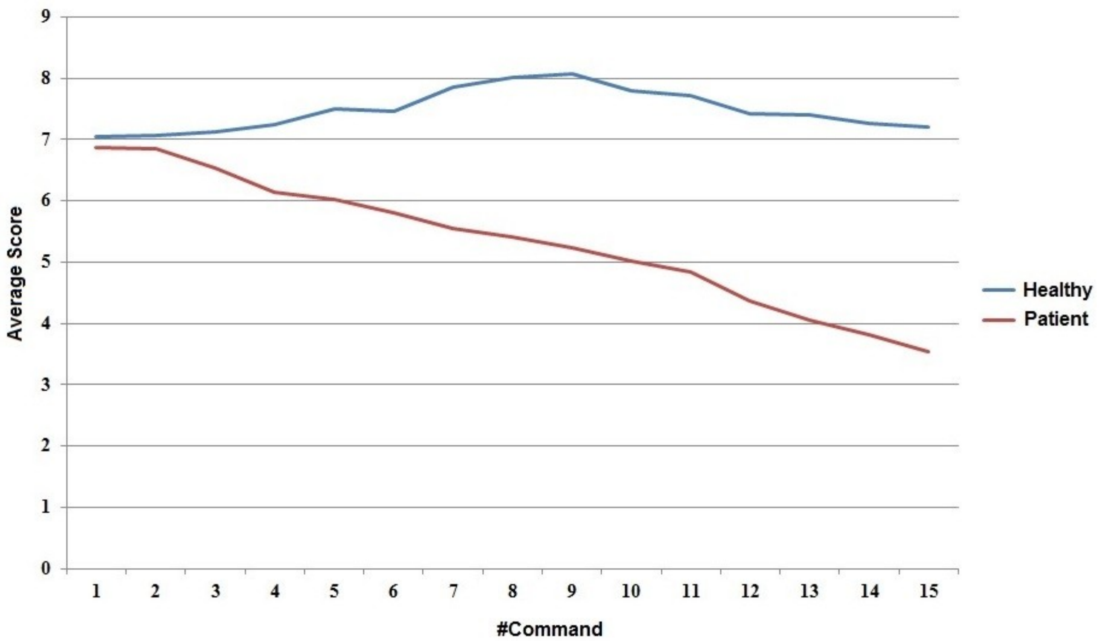


Figure 9) The comparative chart of the average scores for MG patients and healthy volunteers.

Gaze Direction \ Inputs	mv_1	mv_2	mv_3	mv_4	mv_5	mv_6	mv_7	mv_8	mv_9	mv_{10}	mv_{11}	mv_{12}
R	M	M	H	L	L	H	M	M	H	M	L	H
UR	M	M	H	L	L	M	M	M	H	M	L	M
U	M	H	L	L	L	M	M	H	L	M	L	L
ULe	H	M	M	M	L	M	H	M	M	M	L	L
Le	H	L	M	H	L	M	H	L	M	H	L	L
DLe	H	H	H	H	M	H	H	H	H	H	M	M
D	H	H	H	M	H	M	H	H	H	H	H	M
DR	H	H	H	M	M	H	H	H	H	H	M	H

Table 1: Determining the gaze direction based on membership values (mv)

dard deviations are shown in Table 2. The error margins of the healthy volunteers' scores (especially in the medial commands 7 to 11) are somewhat higher, since these scores depend on the strength of the eye muscles [10] that differs from person to person. On the other hand, the higher error margin in the final commands of the MG patients is the result of the various degrees of muscular weakness caused by MG. Apart from these negligible deviations, the performance of the healthy and MG groups are shown to be consistent and declining, respectively.

In summary, we investigated the use of automatic software, which measures the user's ability to keep gazing at various directions, to estimate the risk of Myasthenia Gravis. A fuzzy gaze detection algorithm, which has shown accurate and fast performance on the relevant data sets, is proposed here. Our method can be considered a cheap, safe, and efficient alternative to other expensive and more demanding tests.

The proposed fuzzy algorithm can be further improved by enriching the fuzzy rule base. Moreover, for the inputs μ_i for i=1, 2, 3, 7, 8, and 9 (the upper halves of the eye images), it is important to note that due to the upper curved line of the eye, half of these sections are covered by eyelids and eyelashes. Therefore, as shown in Table 1, these values are often M or H. This inaccuracy can be eliminated by changing the fuzzy membership functions for the above values via expanding the horizontal axis.

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#Command	Scores of Healthy People		Scores of Patients	
	Mean	Error Margin	Mean	Error Margin
1	7.05	±0.01	6.88	±0.01
2	7.06	±0.01	6.85	±0.01
3	7.13	±0.01	6.54	±0.01
4	7.24	±0.02	6.14	±0.01
5	7.51	±0.02	6.03	±0.01
6	7.46	±0.02	5.81	±0.02
7	7.86	±0.03	5.55	±0.02
8	8.02	±0.03	5.41	±0.02
9	8.07	±0.03	5.24	±0.02
10	7.80	±0.03	5.02	±0.02
11	7.72	±0.03	4.84	±0.02
12	7.43	±0.02	4.36	±0.02
13	7.41	±0.02	4.05	±0.03
14	7.27	±0.02	3.81	±0.03
15	7.21	±0.02	3.55	±0.03

*confidence interval = 95%

Table 2: Details of the score distribution

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