The Fischell Department of Bioengineering
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November 8, 2021

Office of Orphan Products Development
Food and Drug Administration
WO32-5271
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Ladies and Gentlemen:

We propose to submit an application to develop a vivo diagnostic model to effectively create a metric by which the rare neurological disorder Visual Snow Syndrome's severity can be quantitatively measured in patients. Visual Snow Syndrome (VSS) was only identified as a unique disorder approximately ten years ago and is largely unknown in terms of factors that may cause the disease. The goal of this device will be to provide an accurate diagnosis for those with the condition, beyond simply ruling out all other potential disorders as well as recording the intensity of the symptoms.

The proposed device is a computer program which will utilize the Snellen eye chart, commonplace in optometry offices with the intended purpose of determining an individual's visual acuity and overlay an adjustable layer of static at varying intervals on the eye chart. The amount of static will be adjustable, ranging from very mild cases to extremely severe. Patients will then be able to pinpoint a precise level of static within their visual field. These metrics will provide an objective and measurable baseline for sufferers of the disorder, which could help primary care physicians aid individuals afflicted with the condition.

Currently a VSS diagnosis requires an individual to possess two of the following: palinopsia (after images), enhanced visual phenomena (floaters, blue field entoptic phenomena, etc.), photophobia (sensitivity to sunlight/bright lights), nyctalopia (night blindness). The two distinct categories of VSS are broadband (entire visual field) and pulse (flashing orbs). Other commonly associated symptoms include migraines. There are currently no approved methods to diagnose or treat VSS beyond migraine medications which offer limited effectiveness in a small subset of patients.

From a clinical standpoint, our aim is to launch clinical trials of this device on a large group of patients, to gather valuable data. As a disorder with underfunded research and little to no answers for those afflicted with this debilitating disease, we hope to offer tangible results and push the conversation to the forefront of rare diseases. Although the exact number of individuals afflicted with this disorder is unknown, it is safe to assume there are less than 8000 VSS patients in the United States. With no objective method of determining an individual's symptoms, it is left to the individual to be self-aware, and realize the visual disturbances they are seeing daily are not

normal. While the disorder is not degenerative, that does not make the symptoms any less difficult or more manageable. This project, to objectively quantify VSS symptoms, is the first step towards finding a cure for this debilitating disorder.

Sincerely,

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Request for Humanitarian Device Designation:

Medical Application for Aid to Diagnosis Device for Visual Snow Syndrome

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Indication for Use

Intended use of the device

As a aid to assessing impairment of vision in central processing disorders by quantitative addition of visual noise to images used to measure visual acuity and perception.

Indication Statement

As a tool to assess the character and severity of endogenous visual noise by overlay of exogenous visual noise on visual acuity in patients with Visual Snow Syndrome.

Background Information about Visual Snow Syndrome

Definition

Visual Snow Syndrome (VSS) is a a central nervous system disorder that degrades an individual's visual acuity. To have a diagnosis of VSS, a patient must have an overlay of small black and white dots across their visual field, commonly referred to as visual static or snow, for at least three months.[1] These dots are made increasingly more disturbing to a patient when exposed to bright or flashing lights, as well as other erratic visual stimuli. The constraints for VSS are classified as having the presence of two of the following four symptoms: palinopsia (after images), enhanced visual phenomena (floaters or blue field entoptic phenomena), photophobia (light sensitivity), and nyctalopia (night blindness). Palinopsia is defined as trailing images, or after images. After images are essentially a silhouette of an object when an individual moves their head. A common example is if one were to stare into a camera flash, and they saw the flash imprinted on their visual field, even on the backs of their eyelids. Trailing images are in essence a series of a stationary object when an individual moves their head.[2] Floaters are defined as small nondescript entities that appear in a patient's visual field, oftentimes when they are exposed to changing lighting conditions.[3] Photophobia is the extreme discomfort when an individual enters a well light environment. This is commonly associated with tears and seeing a series of bright white spots. Nyctalopia, or night blindness, which is the extreme difficulty to see in low light conditions makes any activity that takes place in the dark very difficult.[4] Migraines are a common non-visual symptom as well. What causes discomfort for one patient may drastically vary from patient to patient, as this disorder is largely individualized, with several overarching constraints which determine if one is truly afflicted with the disorder.

Figure 1. Depicting floaters in the eye[5]

Floaters are small proteins that reside within the vitreous of the eye. Floaters are only visible momentarily and are associated with the eye's adjustment to changing lighting conditions. Floaters are not unique to VSS, but patients complain of having them much more frequently than the average person.

Figure 2. Unimpaired vision compared to nyctalopia[6]

The image above is a display of nyctalopia, which clearly highlights the disparity in visible foreground in the two images above. Nyctalopia makes everything from driving to walking extremely dangerous in low light conditions. Nyctalopia is considered a visual processing issue, as the photoreceptors within the retina are unresponsive to the low light stimuli, causing the patient's vision to be almost entirely obscured.

Classification

There are two subsets of VSS, referred to as pulse and broadband. Pulse is characterized by flashing orbs of white light, while broadband is an evenly distributed layer of static across a patient's visual field. The intent of this research is primarily focused on the broadband classification of VSS.[7]

Figure 3 Visual representation of several symptoms of Visual Snow Syndrome[8]

In the diagram above, various symptoms and combinations of visual disturbances are shown. Image A is a photo of unimpaired normal vision. Image B depicts the standard broadband classification of VSS, with static encompassing the entirety of the visual field. Image C is a display of palinopsia and after images. Image D includes floaters and photopsia. Image E is a photo of nyctalopia. Image F is a hypothetical combination of what a VSS patient's vision could look like at any given time.

Clinical Categorization

Both classifications of VSS are treated the same. It is unknown if there is a difference in the causation of the disorder or prevalence of underlying symptoms between pulse and broadband patients. It is subjective as to how disruptive the disorder is perceived.

Treatment Options and Outcomes

There are currently no approved diagnostic measurements or proven treatment methods for VSS, in existence. The following are minor solutions that may provide patients with mild improvement of symptoms.

Tinted sunglasses in varying colors have proven to temporarily mitigate light sensitivity in patients.

Although there are no approved medications prescribed to treat VSS, doctors will recommend migraine alleviating medication in some cases. Lamotrigine, Mirtazapine, Topiramate, Valproate, in addition to other medications intended for migraine reduction have been prescribed to patients. It is important to note the medications being prescribed to patients are not FDA approved, nor have they been proven to reduce symptoms. The medications that are prescribed to patients are primarily done on a guess and test premise of extremely limited statistics.[9] Occasionally mild improvements occur in a select group of individuals, but side effects such as severe skin rashes, and a lack of sufficient successful outcomes outweigh the potential benefits. Before any form of medication can be approved, data is needed. It is impossible to discern if medications of any sort could be beneficial without a quantitative metric.

Patients must largely discern what is most bothersome and avoid situations that could prompt adverse reactions.

Description of the Device

The proposed device is a software device that enables quantitative manipulation of an image displayed on an electronic video monitor. The type of manipulation is introduction of noise pixilation to the image. This imaging noise resembles viewing the image as through a snowstorm. The pixelized "snow" can be independently adjusted with respect to pattern of distribution, particle density, particle size, color, brightness, contrast, and sharpness. The background image is arbitrary and may range from standard visual metric tools such as a Snellen Eye Chart to a photograph from nature or a person's face.

The purpose of this device is to enable grading of the severity of "visual snow" on acuity by the conduct of a sensitivity analysis about the variables of induced visual noise. For example, if a patient exhibited an acuity score of 20/40 before the introduction of exogenous noise, and then worsened to 20/50 depending on the setting for the variables of the exogenous "snow", then the patient's condition could be characterized based on the specifics of the software settings. The exogenous "snow" variables and their settings are expected to offer additional insight into the nature of the specific disorders of CNS image processing for each patient. Since the manipulation of exogenous noise is quantitative and objective, the information derived from this testing can be conveyed between clinical professionals. It enables tracking longitudinally throughout a patient's course and categorization of findings between patients.

The following images illustrate the manner in which images can be manipulated using the software device we propose here.

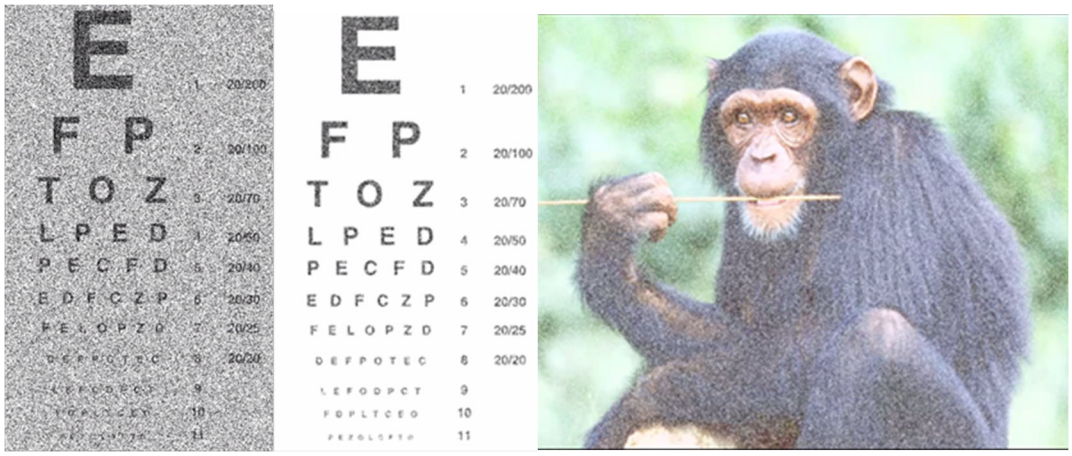

Figure 4. Examples of image manipulation using the software device.

The Snellen Chart on left and center of Figure 1 were degraded so that black letters incorporated a random white snow pattern against a background with variable brightness and black/white ratios. The chimpanzee image on the right illustrates how a physically relevant image is degraded by specific settings on the software variables, thereby altering the patient's ability to perceive the image.

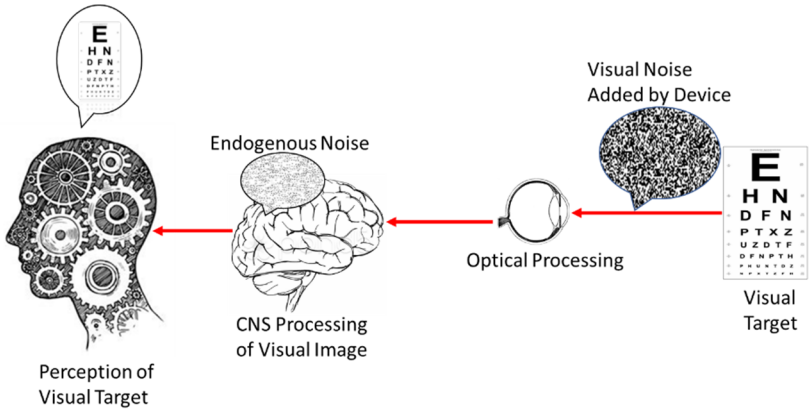

Figure 5. Schematic indicating multiplexing of visual noise from proposed device with internal noise and image of a visual target

Scientific Rationale For Its Use As Proposed

The scientific rationale for the proposed device is based upon established mathematical methods of signal processing. In the setting of Visual Snow Syndrome, an image in the environment is perceived after optical details are resolved in the retina and then processed in the central nervous system to enable cognitive perception of the image. When noise is either spuriously introduced at some stage of CNS processing or exogenous noise is amplified, perception of visual images is reduced. A key question then becomes whether incorporating visual noise to the image before CNS processing will result in simple addition of noise signals as in linear system or whether this results in a more complex disorganization of perception. For example, periodicity in the CNS noise that may be inapparent to the patient may be more readily identified by introducing periodic noise on the visual image. Statistical patterns in CNS noise may be revealed by addition

of various distributions in noise intensity, e.g. gaussian, random binary, pseudo random pattern, etc.

At present, the noise in Visual Snow Syndrome cannot be quantitatively characterized. Our proposed device will provide quantitative metrics to inform clinicians about the severity and quality of signal CNS processing of visual images. For example, to understand the aspect of the CNS responsible for VSS as an engineering system we stimulate the system with controlled signals like the normal operating conditions. The exogenous noise that we apply to our test images have a spectrum (Fourier components) in the frequency domain like the perceived noise originating from the brain. Our exogenous noise may be abruptly turned on or off, as a step function. The amplitude of this step-signal stimulation can be varied as can the direction of of signal e.g. white vs black pixelation. In addition, our device stimulus can deliver as much signal power to the CNS visual system as necessary.

For a unidimensional signal, the crest factor (c_f) describes the ratio of peak values to the effective value, or the extremeness of the peaks in a fluctuating waveform.

$$c_f^2 \equiv \frac{\max_t u^2(t)}{\lim_{N\to\infty} \frac{1}{N} \sum_{t=1}^{N} u^2(t)}$$

Equation 1. c_f is the ratio of the peak magnitude of peaks relative to the square root of the mean squared value where u(t) is the vector orthogonal to the signal movement in time. In a visual target, the c_f may be computed as a spatial integral over the region of interest.

In some respects, our proposed device will enable analysis of visual noise as is conducted for clinical evaluation of endogenous auditory noise, i.e. tinnitus.[10,11] Individuals with tinnitus are placed in a soundproof room, and wearing noise cancelling headphones. The patients are exposed to a series of random words, sounds, clicks, beeps, and other noises at a variety of different volumes to determine which auditory signals improve or worsen the symptom of tinnitus.

Possible Modes Failure and Mitigations to Assure Safety

As with any device to aid diagnosis, there is a potential to miss or misidentify symptoms. Clinical studies are needed to understand the sensitivity and specificity of our device. Since our device is noninvasive and without lasting physiologic effects, the risk to patients is small. Furthermore, the information provided by this device is to quantify symptoms rather than to establish a diagnosis, so risks to patients who are exposed are minimal.

To verify performance and usability of our device we intend to follow FDA guidance for software, mobile medical applications, quality system regulation, design controls and human factors analysis.

Future Plans

Our device, as currently proposed to measure and monitor symptoms of VSS, is the first step in enabling treatment. At present, there are no approved drugs or medical devices indicated for management of VSS in part because clinical studies cannot be designed without a validated metric to assess clinical benefit. Therefore, once we have validated our device as an objective yardstick, we intend to enlist clinicians with an interest in VSS to conduct systematic clinical studies using the various treatment modalities offered by different clinical sites that are all now being administered off-label. Our long-term goal is to identify a treatment regimen that can be approved as safe and beneficial.

Population Determination: Visual Snow Syndrome is a Rare Disease

Prevalence and Number of Patients Treated per Year in the United States

A key question with respect to determining the regulatory pathway for this device, is an estimate of the number of patients in the United States who are treated for Visual Snow Syndrome annually. Various small case series of VSS suggest that the disorder is rare. Few centers in the US have specialists that have significant clinical experience in managing the disorder. In fact, VSS was only first reported as a specific entity as recently as 2013. The specific findings and symptoms associated with VSS continue to be refined and it remains unclear whether VSS is represents a single disease entity, a constellation of CNS disorders, or is itself a subset of a broader class of pathophysiology. Moreover, there appears to be diversity of interpretation of symptoms among clinical specialists because there is no established methodology to categorize patients, or track progress in those diagnosed with the disease. The National Organization of Rare Diseases considers Visual Snow Syndrome to be a rare disorder and states that its website states that its prevalence is unknown. Some patients with early or mild disorder may not engage a clinician who is sufficiently expert to diagnose their condition, further complicating assessment of prevalence.

One effort to understand VSS prevalence utilized a crowdsourcing platform to capture patients in the UK who had prior knowledge of VSS, an interest in their health and access to web-based surveys. Of 1015 volunteers who enrolled in the study, 22 patients were determined on by a web-based survey to have VSS. By extrapolating the incidence in this study sample to the entire population of the UK, the authors concluded that as many as 1.4 million patients in the UK have VSS! We believe this extrapolation is grossly inaccurate. Even though the UK lacks the diversity of the US population, we would expect millions of patients to present for treatment in the US if VSS were as prevalent as the crowdsourced population study suggests. Crowdsourcing to estimate prevalence should be considered skeptically because enrollment selects for patients who are interested in their own health and willing to seek out and complete online surveys. It does not represent patients who were examined by a physician. Also, the UK study population was drawn from a nondiverse population compared with the US.

Another recent study estimated that the worldwide population of patients with VSS was nearer to 200.[12]

Most published studies of patients with VSS include only a handful of patients and are reported from a few medical centers that specialize in caring for these patients. [13,14,15]

Therefore, while a precise estimate of the number of VSS patients treated in the US annually is unknown, the patient population is expected to be quite small and far fewer than 8000.

Rate of Survival

There have been no reported deaths directly caused by Visual Snow Syndrome and there are no data to indicate reduced survival. However, limitations to vision have been associated with premature death. [16,17]

Summary

The development of a Visual Snow Syndrome device as an in vivo aid to diagnosis will be will benefit the VSS community by improving objective and quantitative assessment of symptoms. There are currently only limited data reported by research groups to date, as no testing in the U.S. has ever been performed on a large enough subject group to extrapolate onto the population at large. We believe that fewer than 8000 patients in the US population are being treated annually for VSS and that no significant medical advancements have become available in diagnosis or treatment made since the first case was reported in 2014. A key scientific limitation to progress has been the absence of a validated metric to assess clinical benefits of treatment or progression of disease. VSS is a serious and debilitating disorder. Therefore, HUD exemption for a tool to aid in diagnosis is critical to finding a safe and effective treatment for this rare disease.[18].

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