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PERSPECTIVE

A new tool for monitoring brain function: eye tracking goes beyond assessing attention to measuring central nervous system physiology

Concussion and other forms of brain injury are not always detectable with conventional means such as radiographic imaging. The lack of accurate diagnostics, biomarkers, and outcome measures has a devastating impact. Individual patients may suffer in obscurity, self-medicate into an addictive spiral, have impaired professional activity, and develop failed interpersonal relationships.

Without accurate diagnostics, it is impossible to know the incidence of concussion or assess its societal impact. Though numerous studies have investigated neurologic deficits, and factors ranging from executive functioning, completion of daily activities, return to work/school, language, reading and other specific impacts of concussion, there is still no broadly accepted definition for concussion and no objective diagnostic. The lack of appropriate classification schemes and objective outcome measures for patients entering clinical trials for concussion and other forms of traumatic brain injury (TBI) contributes to the failure of such trials for therapeutics and prophylactics at great expense to the research and development community and those it hopes to serve, including athletes, students and hapless victims of trauma.

Recently we published two manuscripts describing a novel algorithm for eye tracking that will be useful for concussion, other forms of TBI and other neuropathologies (Samadani et al., 2014; Samadani et al., 2015). Eye tracking assesses brain function rather than appearance or electrical activity, and thus represents a relatively newer modality for assessment of central nervous system integrity. The difference between the two papers published by our group and nearly all prior eye tracking publications, is that these new papers utilize non-spatially calibrated eye tracking. Rather than assess what someone chooses to look at, the tracking measures how well the eyes are capable of moving.

Spatially calibrated tracking has limitations: For more than 30 years, spatially calibrated eye movement tracking technology has been widely used for marketing studies, video games, and neuropsychiatric research. Progressive supranuclear palsy, dementia, schizophrenia, amyotrophic lateral sclerosis, post-concussive syndrome, autism and Fragile X are among the numerous diseases with characteristic eye tracking anomalies detectable with such tracking. Limitations of the technology arise from subject fatigue, visual and other attention deficits, and distraction.

The use of spatial calibration for eye tracking makes two assumptions. The first is that the eyes are physically capable of moving to a particular extent. The second is that the eyes are moving together. Calibration involves asking the observer to look at a series of high-contrast dots that appear sequentially around the perimeter of the monitor. The eye-tracker determines whether the volitional movements to the dots are consistent and accurate enough to define a function that transforms the raw pupil-angle measurements into meaningful spatial coordinates. Calibration requires subject cooperation, which may be extremely variable even in the same person tracked at different times, let alone among different people with different motivations. Calibration also requires vision and intact functioning of the cranial nerves moving the pupil. It is this latter requirement that has, until the publication of our papers, limited the utility of eye tracking to conditions that do not affect this basic activity.

The reason that calibration prevents detection of subtly abnormal eye movements is that if one eye has weakened movement in a particular direction, the camera will interpret the eye's ability to move in the direction of that weakness as the full potential range of motion in that direction due to the calibration process. For example, if during calibration, a person is directed to look at a position but only moves halfway there, the calibration algorithm will mistakenly indicate that movement to the halfway point is actually full movement. Subsequent eye movements to the halfway point will be interpreted as occurring at the full range of normal motion. Thus, though one eye only makes it half-way to the target, while the other eye is fully there, the camera will interpret both eyes as being together when one moves only half the distance as the other (**Figure 1**). While it is possible to separately track each eye to detect abnormal motility, this is a suboptimalapproach as it requires a dichoic apparatus, if one wishes to compare the pupil positions over time, and a subject capable and willing to endure the calibration process twice.

Non-spatially calibrated tracking uses time rather than space: Recently we described a novel technique for the measurement of high-resolution (500 Hz) eye movements without need for spatial calibration. The technique consists of having a subject using a chin and forehead rest view a monitor on which a short film clip plays continuously inside an aperture that moves around the perimeter of the screen. The pupils are tracked over 220 seconds of time for comparison to each other and to a database of control subjects. The technique does not require a trained examiner and is fully automatable.

The challenge of working with uncalibrated data is how to determine whether a given eye-movement trace results from an observer's engagement in the task, as opposed to artifact, random eye movements, or deliberate eye movements unrelated to the task. By looking at the eye movement trajectories in the time domain rather than the spatial domain, we can quantify spatiotemporal measures that do not rely on spatial calibration (**Figure 2**). Further the limitation of drift following calibration in brain injured subjects is avoided, since no calibration is performed and if drift was to occur, it would likely affect both eyes equally, rendering comparisons between the eyes still valid.

We demonstrated that this methodology enables direct assessment of the physiologic function of cranial nerves III and VI (Samadani et al., 2014). We showed that recording of subject eye movements during watching of a 220 second

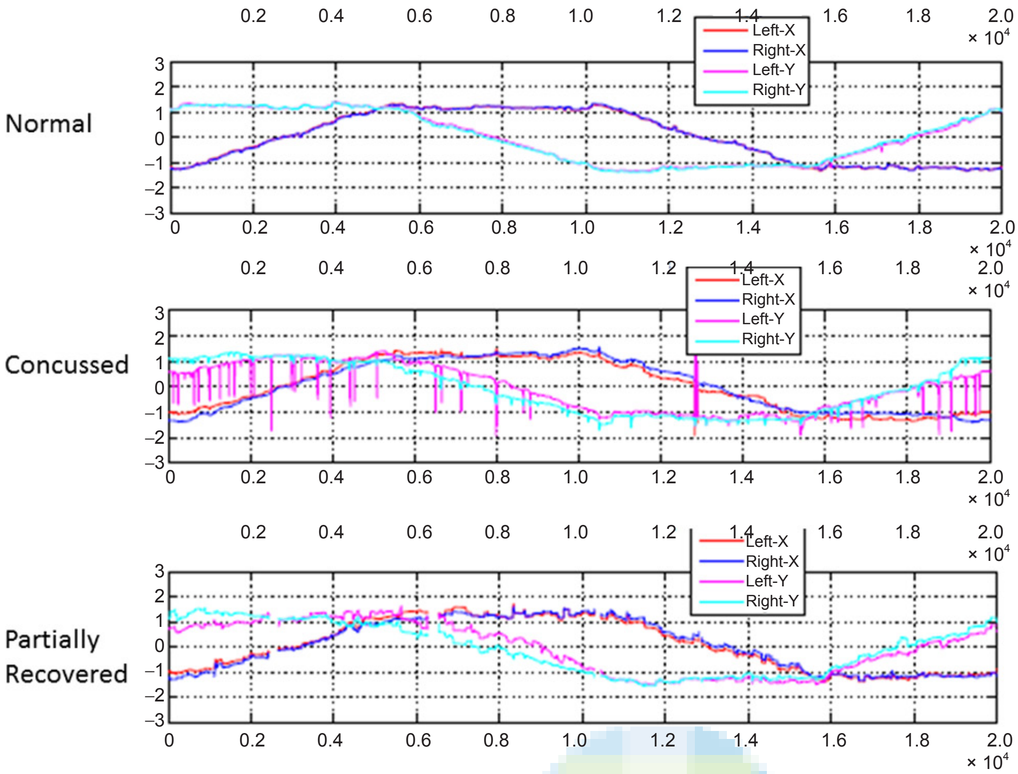

Figure 2 A normal patient has eyes that move together when the Cartesian coordinates are separately plotted over time. A patient with concussion, and partial recovery has eyes less capable of coordinated movement.

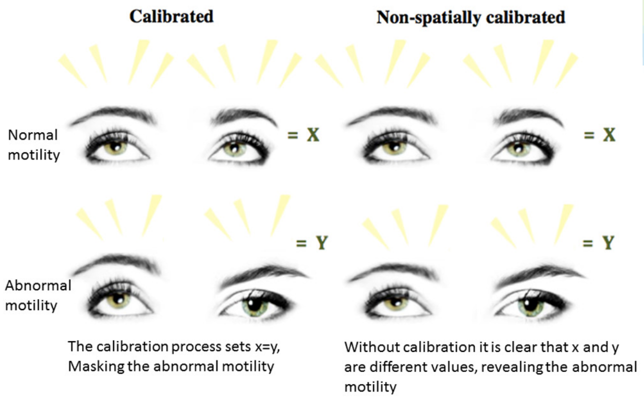

Figure 1 Spatial calibration transforms the amount of light reflecting off the cornea and pupil into a constant value regardless of whether the eye has normal motility, thus masking deficits. Without calibration, abnormal motility can be detected.

music video allows rapid detection of cranial nerve palsies and that these can be tracked through their resolution. Cranial nerve palsies are commonly found in numerous diseases, including trauma, vascular lesions, tumors, diabetes and other endocrinopathies, and infectious and inflammatory pathology among many more.

This technique enables quantitative assessment of any pathologic process impacting the functioning of these cranial nerves and thus creates a new mechanism for assessing physiologic function of the central nervous system by conferring the potential of eye tracking in a clinical context.

This technology is additionally useful for those unable to participate in calibration, such as young children, neurologically impaired individuals, and research animals capable of watching videos.

The obvious utility of such technology is detection of concussion, which has been well-established as impacting ocular motility (Ciuffreda et al., 2007; Goodrich et al., 2013). We demonstrated that (1) eye tracking can detect and quantitate the severity of abnormal eye movements within a few hours after concussion (2) that the severity of abnormal eye movements correlates with the severity of concussion symptoms using two different measures as measured by Spearman correlation and (3) that after concussion eye tracking initially worsens then improves towards normal within one month in most patients (Samadani et al., 2015). We have not yet determined the shortest possible time between head impact and abnormal eye tracking metrics.

The technology we have developed is as passive a task as possible, to limit the impact of volitional factors such as attention and compliance with instructions, which are components of fatigue. When a subject closes the eyes or turns away from the screen, such data (or lack thereof) does not affect analysis results which are only based upon the data that is actually captured. Since the task is relatively passive – the patient is told nothing at all or given the instructions "watch the TV" – there is no requirement that the patient has literacy in any particular language.

Prior spatially calibrated eye technology designed to detect concussion assesses predictive timing which may serve as a proxy for attention (Heaton et al., 2014).

The concept of disconjugate gaze as a marker for brain injury has its origins in the oldest known surgical treatise (Kamp et al., 2012). Textbooks and chapters on brain injury have been dedicated to assessment of eye movements, and a pubmed search of brain injury and eye movements yields 477 citations. Spatially calibrated eye tracking assessing rigorous optometric measures in cooperative patients demonstrates eye movement abnormalities in patients with post-concussive syndrome relative to uninjured controls (Heitger et al., 2009; Cifu et al., 2015).

Assessment of binocular gaze conjugacy in primates for research purposes has been performed for many years with the magnetic search coil technique requiring coils implanted into the bulbar conjunctiva. This technique was first described by Fuchs and Robinson in 1966 and can also be performed in humans fitted with sclera search coils designed specifically for tracking eye movements. Experimentally, spatially calibrated eye movement tracking using the Bouis oculometer, which requires that the head is rigidly fixed, shows that healthy seven year old children have increased disconjugacy of eye movement during saccades relative to adults while both perform a reading task (Bucci and Kapoula, 2006). Research on disconjugacy during reading can be performed using a dichoptic apparatus in which the individual eyes are spatially calibrated separately and presented with stimuli to assess movements separately for simultaneous comparison to each other (Schotter et al., 2012). The advantage of our technique over these well-established and rigorous methodologies is that our algorithm can be automated, and performed simply, remotely, and non-invasively, in the absence of a trained technician.

Our methodology assesses physiologic functioning of the central nervous system and thus provides different information about the brain than imaging studies enabling visualization of anatomy or electrical studies of activity. The closest proxy for eye tracking will likely be the “follow my finger” component of physical examination that assesses sustained vergence, or the ability of both eyes to converge on a single moving focal point.

Non-spatially calibrated ocular motility tracking assessment does not require that the subject explicitly consent to being tracked prior to assessment of their central nervous system functioning, and thus may raise ethical considerations as it can be deployed even remotely via webcam. The potential applications of the algorithm we have devised include improved diagnosis and detection of diseases ranging from internuclear ophthalmoplegia to strabismus, however its greatest initially recognized potential is as a potential outcome measure or biomarker for brain injury and concussion.

The ultimate utility of non-spatially calibrated eye tracking however, will not be established by my undoubtedly biased speculation, or the work of my laboratory group and collaborators. It will be determined by other researchers and clinicians who will, upon replication of our results, agree that brain injury is more vast than visible on conventional imaging, ultimately validating the fears and concerns of the previously undiagnosed and untreated afflicted. Replication of our results will also enable the testing of therapeutics and prophylactics for brain injury, perhaps changing the game for many more potential sufferers. Accurate stratification of patients entering clinical trials for brain injury, and quantitive outcome assessments have been elusive, leading to the failure of 30 consecutive human trials. The need for another outcome measure here is not optional – it is an urgent imperative, necessary to prevent further exercises in futility.

Uzma Samadani*

Steven and Alexandra Cohen Veterans Center for Post-Traumatic Stress and Traumatic Brain Injury at NYU Langone Medical Center; Departments of Neurosurgery, Psychiatry, Physiology and Neuroscience, New York University School of Medicine, New York; New York Harbor Health Care System, USA

***Correspondence to:** *Uzma Samadani, M.D., Ph.D., F.A.C.S., uzma@samadani.com.*

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