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Objectively-based vergence and accommodative dynamics in mild traumatic brain injury (mTBI): A mini review

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ABSTRACT

Vergence and accommodation have been critical areas of investigation in those with mild traumatic brain injury (mTBI). In this mini-review, the major laboratory studies in the area using objective assessment of vergence and accommodative dynamics in this population are discussed. These include the basic findings, their diagnostic and therapeutic implications, potential study limitations, and suggested future research directions. All studies provided important new information, and insights, into the area. There were two key outcomes of the reviewed studies common to both the vergence and accommodative systems in those with mTBI. First, most dynamic parameter's responsivity at baseline was abnormal: it was slowed, delayed, and/or inaccurate as compared to the normative control data. Second, most of the abnormal dynamic parameter's responsivity could be remediated, at least in part, following a short period of oculomotor-based vision therapy, thus demonstrating considerable residual neuroplasticity in the damaged, human brain.

1. Introduction

Traumatic brain injury (TBI) can be defined as "any structural damage caused by an external force to the brain and its associated structures, such as the cranium, resulting in physiologic disruption of brain function" (VA/DOD, 2009). In the United States, it is estimated that 1.7 million people sustain a mild traumatic brain injury (mTBI) each year, at a total cost of 75 billion dollars (CDC, 2016). Furthermore, it is the leading cause of death and disability in the United States (Faul et al., 2010). Hence, TBI is a major social, economic, medical, optometric, and public health concern (Ciuffreda et al., 2016; Ciuffreda et al., 2021).

Due to the global nature of the injury, and the complexity of the brain, it is not surprising that individuals who sustain an mTBI frequently manifest a constellation of chronic deficits of a sensory, motor, perceptual cognitive, attentional, and language-based in nature (Ciuffreda et al., 2016; Ciuffreda et al., 2021). More specifically, many exhibit a range of visual dysfunctions and related symptoms, such as photosensitivity, visual field loss, and visual motion sensitivity, to name a few, as well as those that are oculomotor-based (Ciuffreda et al., 2016; Ciuffreda et al., 2021). Furthermore, given the susceptibility of the brain to insult, in particular the midbrain (Hirad et al., 2019) which is involved in many aspects of eye movements, the presence of residual oculomotor dysfunctions is not surprising. In this paper, the vergence and accommodative systems in mTBI will be reviewed in the context of both the abnormal baseline findings, and their related remediation following vison therapy, using objective assessment metrics.

2. Vergence

The function of the vergence eye movement system is to track objects moving in depth, with the goal of attaining cortical fusion and bifoveation within Panum's fusional areas in a time-optimal manner (Schor & Ciuffreda, 1983; Ciuffreda & Tannen, 1995). The vergence system has four input components: disparity ("fusional") vergence is primary, blur-driven accommodative vergence is secondary, and with proximal and tonic vergence being tertiary in nature under normal binocular-viewing conditions (Ciuffreda, 1992; Hung, Ciuffreda & Rosenfield, 1996).

Dynamics of the normal vergence system have been carefully recorded, quantified, and modelled in the laboratory setting (Semmlow et al., 1993; Semmlow et al., 2019). The overall response time is effectively less than one second, being comprised of approximately a 200 msec latency followed by about an 800 msec motor response. It has been conceptualized and modelled as having dual-mode control (Hung et al.,

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1986; Semmlow et al., 1993). The first 200 msec of the response is comprised of the large, rapid, open-loop, pre-programmed component, whereas the subsequent smaller, slow component functions to obtain fusion under visual feedback control (i.e., closed-loop). This dual-mode concept has important diagnostic and therapeutic implications, which will be discussed later. Lastly, the underlying motoneuronal controller signal has been found to be in the midbrain of primates (Mays, 1984). This signal is composed of a small pulse which functions to control the initial, rapid, open-loop dynamic trajectory, and is followed by a step which functions to control the remaining slow, closed-loop aspect to attain/maintain fusion, hence an overall pulse-step controller once neurally-integrated. This is also believed to be the case in humans per laboratory findings (Hung et al., 1994; Semmlow et al., 2019) and related modelling/computer simulations (Hung, 1998; Semmlow et al., 2019). It has recently been proposed that the rostral superior colliculus functions in this vergence integrator capacity in both monkeys and humans (Rucker et al., 2019).

3. Accommodation

Dynamics of the normal accommodative system have been carefully recorded, quantified, and modelled in the laboratory setting (Schor & Bharadwaj; 2004, 2006). The overall response time is effectively one second, being comprised of approximately a 400 msec latency, followed by about a 600 msec motor response. This system has been conceptualized and modelled as having dual-mode control (Hung & Ciuffreda, 1988), similar to that described earlier for the vergence system. There is an initial, large, rapid, open-loop, pre-programmed component, followed by a smaller, slow sustaining component under continuous feedback control (i.e., closed-loop). And, again, in normals, the research suggests a pulse-step neurological controller (Hung & Ciuffreda, 1988; Schor & Bharadwaj; 2004, 2006). This underlying motoneural controller signal is formulated in the Edinger-Westphal nucleus in the midbrain (Horn et al., 2009).

However, much of what has just been described is abnormal in the individual with mTBI/concussion (Ciuffreda et al., 2016). Hence, the purpose of this paper is two-fold: (1) to review the major studies involving objectively-based vergence and accommodative dynamics in mTBI, and (2) to suggest future research directions with likely fruitful outcomes, to improve our understanding of the basic aspects, and in turn to develop more targeted and efficacious treatment protocols.

4. Laboratory investigations using objective recordings of vergence dynamics in mTBI

There have been five primary studies using objective recording techniques and detailed quantitative analysis in the area. These will be discussed including the major findings, basic and clinical implications, and potential study limitations. Each study provides new and important insights and dimensions into understanding the dysfunctional vergence system in those with visually-symptomatic mTBI.

STUDY 1: The *first* and *largest* investigation was performed by Szymanowicz et al. (2012). A primary goal was to assess dynamic vergence characteristics. There were 21 individuals (aged 24–70 years) with medically-diagnosed, chronic mTBI, and 10 age-match control subjects (aged 18–67 years), with both groups having similar gender ratios. All received a comprehensive vision examination prior to testing and had 20/25 or better corrected distance and near visual acuity. None had constant strabismus. All with mTBI reported typical near vision problems (e.g., intermittent blur and/or diplopia). Symmetric convergence and divergence responses were assessed using the video-based PowerRefractor II (Plusoptix Inc., Atlanta, GA, USA) under binocular-viewing conditions. It has a sampling rate of 12.5 Hz, which satisfied the Nyquist criterion. Resolution was at least 0.9 degs. Targets were comprised of small (0.28 degs.) LEDs positioned along the midline at 1 m and at 0.3 m presented at random times (every 3–7 secs) to minimize prediction, and producing a total vergence stimulus demand of ~7 degs. Room illumination was subdued (2.8 lx).

Typical findings are presented in Fig. 1 from a subject in each group. Responses were fit with a decreasing exponential having goodness of fits ranging from 0.78 to 0.91. Responses were accurate in both groups. However, the mean dynamics were significantly different: they were delayed, slowed, and more variable in those with mTBI. On average, peak velocity was reduced by ~50%, latency was increased by ~50%, and both the response time constant (i.e., time to reach 63% of the final exponential response amplitude) and steady-state variability were increased by ~200%. This was also true for the individual subjects. These abnormalities are likely to have an adverse impact on one's quality of life, both vocationally and avocationally, especially for near tasks such as reading (Thiagarajan et al., 2014).

The results clearly demonstrate the considerable and pervasive abnormalities in vergence dynamics in those adults with chronic mTBI. They suggest both neurosensory processing delays and abnormal motoneuronal control. The 100msec increase in latency is likely too long to be attributed solely to any diffuse axonal damage, hence it may be compounded by an attentional component, as general/visual attention is typically compromised in this population (Yadav & Ciuffreda, 2015). In contrast, the motor abnormalities suggest deficits in the midbrain pulse-step controller signals. The pulse may be either too small and/or have reduced duration, thus resulting in a slowed dynamic trajectory. The step, on average, is of the appropriate size but reflecting either a gain instability and/or increased neural noise, thus resulting in increased steady-state variability but with overall mean accuracy and fusion of the target. Thus, for any vision rehabilitation program, *both* the pulse and step components require targeted treatment protocols to "rehabilitate" both the fast and slow vergence system responses, as has been proposed (Szymanowicz et al., 2012) and described later.

There were three potential study limitations. First, while the sampling rate (12.5 Hz) was sufficient, a higher rate (e.g., 100 Hz) would be better to detect and resolve any small, rapid dynamic response variations, as well as to attain a better estimate of latency. And, a higher rate would be required to detect the 1 or 2 saccades that typically occur during vergence with their very short 30–40 msec duration. Second, brain imaging was not performed, which would have provided insight into the specific neural sites underlying the multiple abnormalities. Third, the system's positional resolution was relatively low.

STUDY 2: The second major investigation was performed by Thiagarajan and Ciuffreda (2013). It was the *first* formal clinical trial to assess the effects of conventional neuro-optometric rehabilitation/oculomotor-based vision therapy on the abnormal vergence dynamics as found in those with mTBI, as described in Study 1. There were 12 individuals (aged 23–33 years) with medically-diagnosed, chronic, mTBI. All reported typical near vision symptoms (e.g., intermittent blur). The appropriate sample size was calculated using power analysis. Testing was the same as described earlier in Study 1, except that vergence latency was not assessed.

Following testing of baseline vergence dynamics, the rehabilitative component was initiated. This involved a crossover, interventional experimental design, single-blind, with a placebo. Thus, each subject served as their own control negating undesirable intersubject variability, and in addition, each subject received both the presumed effective ("real") therapy and the presumed placebo ("sham"). The design had the following phases: baseline measurements; treatment A for six weeks; repeated measurements; treatment B for 6 weeks; repeated measurements, for a total of 16 weeks of engagement. Total treatment time for vergence was 3 h (15 mins/session; 2 sessions/week). They also received a total 3 h of accommodative therapy and 3 h of versional therapy, which is beyond the scope of the present report. The vergence training was performed at 40 cm (2.5 m angles; ~7 degs total) along the midline (i.e., "relative" symmetric vergence). For "step" vergence training of the *fast* vergence system, base-out and base-in prisms were rapidly introduced, with the powers increased and target size decreased

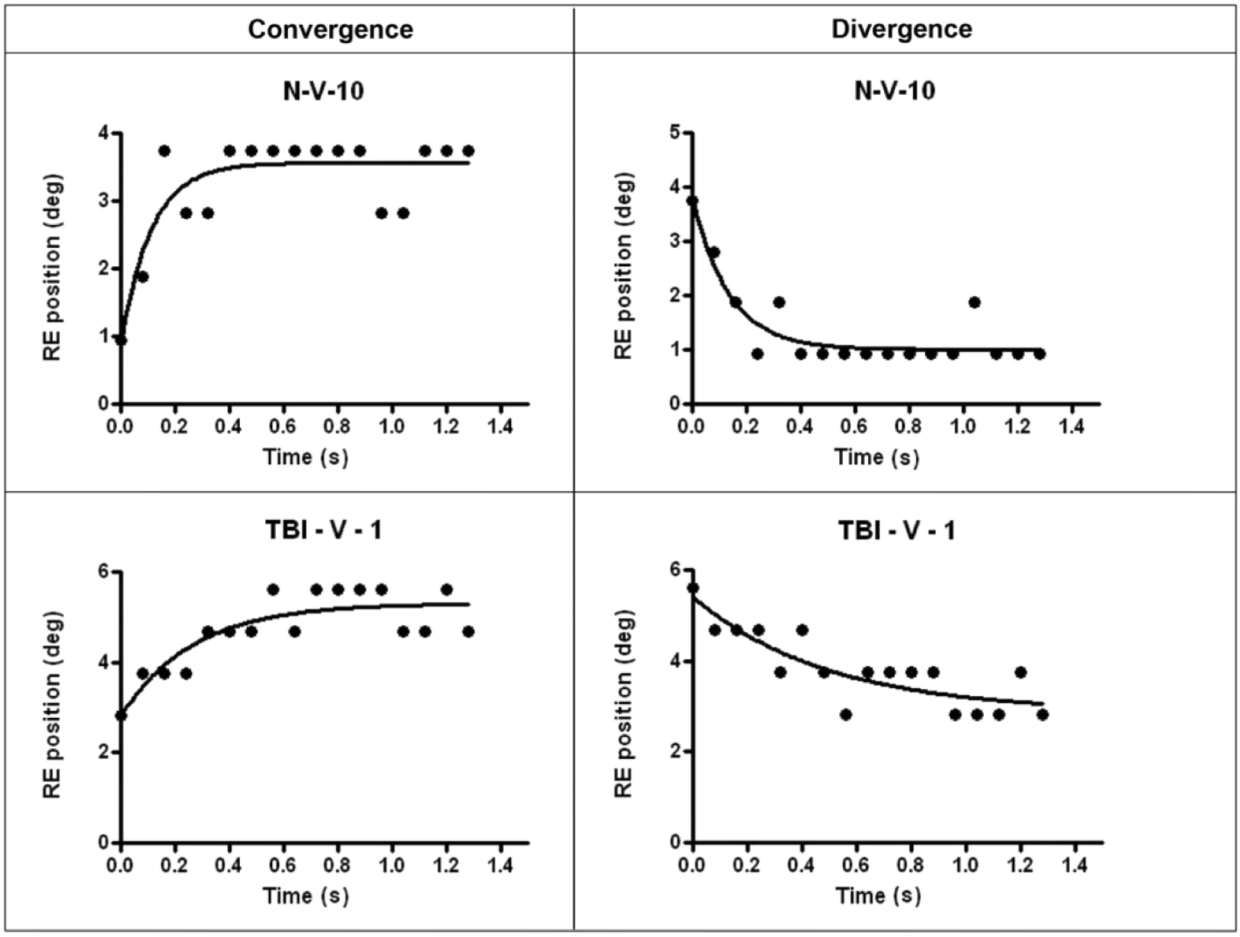

Fig. 1. Sample data and best fit exponential for convergence and divergence responses in a control subject (N-V-10) and subject with mild traumatic brain injury (TBI-V-1). Horizontal eye position. RE = right eye, V = vergence. (Adapted with permission, Szymanowicz et al., 2012).

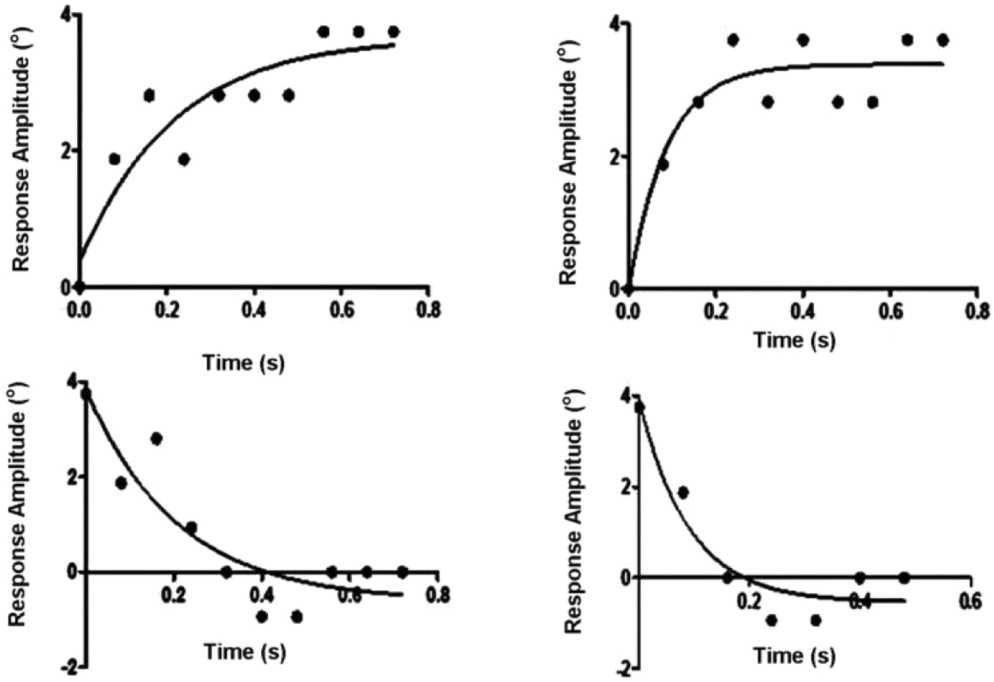

Fig. 2. Horizontal eye position as a function of time. Exponential fit of step vergence dynamic trajectory from the right eye before (left column) and after (right column) oculomotor training for convergence (top row) and divergence (bottom row) in a typical subject with mild traumatic brain injury. (Adapted with permission, Thiagarajan & Ciuffreda, 2013).

as responses improved. For training of the *slow* vergence system, the above "reflex" vergences responses were maintained for 15–20 s. In addition, actual ramp vergence stimulation was used over a range of 0.5–2.0 m angles, with rates changing from 0.1 to 1.0 Hz as responses improved. Lastly, there was a placebo component which mirrored the presumed training components, but which did not include any actual disparity vergence stimulation. All subjects believed that the placebo was a true training component.

The results were interesting. First, baseline vergence dynamics for both convergence and divergence were slowed by up to 50%, and more variable, thus confirming the Syzmanowicz et al. (2012) findings (Study 1). Second, and most importantly, all group vergence dynamic parameters significantly improved following training, except for divergence steady-state variability. Thus, in general, all responses were now faster and with less convergence steady-state variation (Fig. 2). For example, mean peak convergence velocity was 13 degs/sec. at baseline, and it significantly increased to 18 deg./sec. following training. All responses were accurate both before and after training, and they were now completed in approximately 1.5 s. However, while nearly all parameters significantly improved, they did not normalize, presumably due to the very short vergence only training period of 3 h. For example, the post-training convergence peak velocities were still below the normal main sequence values (Hung et al., 1994). Responses were accurate but still slowed. There was also a significant pre-/post-correlation between convergence and divergence peak velocity (Thiagarajan & Ciuffreda, 2014a). Lastly, there were no significant effects for any of the parameters following the placebo training ($p > 0.5$).

The findings clearly demonstrate considerable visual system plasticity in these adults with chronic mTBI. The positive effects could not be attributed to natural recovery, as all were tested 1–10 years following their most recent head injury. Fig. 3 presents a proposed neural mechanism underlying the training improvements: it includes increased synaptic strength, increased number of synapses, improved response neural correlations, and/or more synchronous firing rates in the midbrain controller and elsewhere. This information awaits future studies including brain imaging for confirmation of the specifics.

There were six potential limitations to the study. First, sample size was small, but appropriate per the power analysis. Second, the total vergence training time was very short (3 h), much less than is typically performed clinically in such patients (10–15 h), which likely accounts for the lack of response normalization. Third, brain imaging was not performed before and after the visual intervention to determine the abnormal sites and their subsequent correlated changes. Fourth, while there was a 3 and 6-month follow-up assessment for the clinical parameters (e.g., near point of convergence), which showed persistence of the positive training effects, it did not include the objective laboratory aspect (Thiagarajan & Ciuffreda, 2015). Fifth, the vergence training likely indirectly included a transient, blur-driven, vergence-accommodative component, and hence was not "pure" disparity vergence (Ciuffreda, 1992) per se but rather "relative" disparity vergence; however, the training mirrored that which is performed clinically. Sixth, positional resolution was relatively low.

***STUDY 3*:** In this pilot investigation performed on 5 subjects by Scheiman et al. (2017), the researchers essentially confirmed the earlier laboratory results (Szymanowicz et al., 2012; Thiagarajan and Ciuffreda, 2013), which is important. The unique aspect was that their

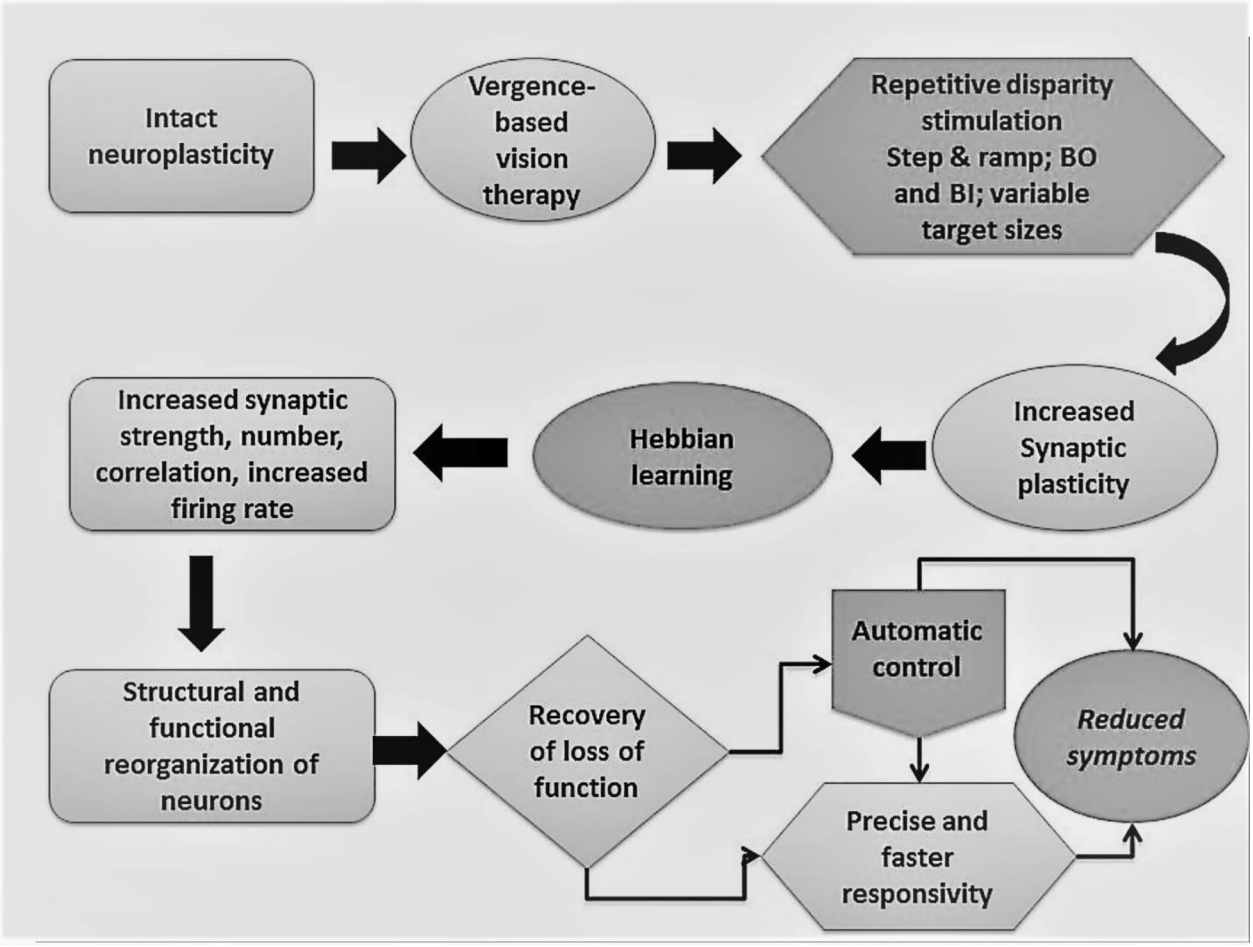

Fig. 3. Proposed underlying mechanisms of vergence-based oculomotor rehabilitation (OR). BI = base-in, BO = base-out. (Adapted with permission, Thiagarajan, 2012).

subjects were medically-diagnosed with mTBI/concussion *and* optometrically-documented with convergence insufficiency (CI), whereas in the earlier two investigations, not all subjects met the criteria for CI, but all did have a receded near point of convergence and many other typical vergence deficits. Conventional oculomotor-based vision therapy, including vergence and accommodative aspects, was performed over a period of 12–20 weeks based on the investigator's endpoint criteria. Therapy was performed both in the laboratory (9–15 h) and at home (14–25 h) in the 5 subjects ages 13–28 years. There were some improvements over the previous two studies: the eye movement instrumentation (ISCAN RK-826CI, Burlington, VT, USA) had a higher sampling rate (40 Hz filtered); a difference of Gaussian (DOG) target was used producing disparity-only vergence stimulation without any blur-feedback related to vergence-accommodation; and the recordings included both position and velocity traces. Recording time was 3–5 secs. Symmetric disparity step stimuli of 4 degrees total were used. Prior to therapy, the typical dynamic vergence deficits were present. Following therapy, convergence peak velocity increased and/or normalized, and convergence accuracy improved considerably. Latency did not change, as it was normal at baseline (~200 msec). Four of the five subject reported significantly reduced near visual symptoms per the CISS questionnaire (Rouse et al., 2009).

However, some of the responses were unusual. For example, in the one subject who they indicated manifested the greatest pre-therapy vergence impairment, the convergence response to the step input was very slow (~0.6 degs./sec.), and ramp-like, over the 3 s recording period shown; furthermore, it was only 2 degs. in amplitude, thus exhibiting a 50% positional error. It were as if the neural signal was pulse-LESS with only a step component; if true, when input to a "pure" neural integrator (but not into a typical "leaky" integrator), a ramp motor output would be produced. This is an intriguing finding that requires confirmation. However, more interestingly, it appeared to normalize following training.

There were five potential limitations to the study. First, sample size was small despite being labeled "pilot" in nature. Second, brain imaging was not performed. Third, some of the responses were unusual and were not provided with any possible detailed explanation. Fourth, there was no follow-up to assess for persistence on any therapeutic effect. And, fifth, it included both pediatric and adult subjects combined in which age-related developmental changes might be a confounding factor.

STUDY 4: While not a laboratory study per se, a recent, detailed, and unique clinical case report by Rucker et al. (2019) provides considerable insight into the area, including both MRI brain scans and objective eye movement recordings. The patient was a 48-year-old female who sustained a brain injury over the left, posterior occiput 11 years earlier, without loss of consciousness. She was medically-diagnosed with mTBI. Symptoms over this 11-year period included, and remain: reading problems, intermittent blur, pain at the site of impact, nausea, dizziness upon head rotation, and balance problems: none of these were present before the head injury. A range of vision-based therapies (e.g., prisms) yielded little success. The objectively-based, vergence responses at the most recent neurological examination were interesting: while there was apparent normal convergence initiation, it was followed by the repeated inability to sustain convergence. This suggests a normal fast but not slow vergence system. The MRI findings, which were performed both at the time of initial insult and at the most recent neurological examination revealed: abnormalities at the right pulvinar in the caudal thalamus, the pretectum, and the rostral superior colliculus. It was the last anatomical site that was consistent with, and was speculated to explain, her abnormal convergence sustaining responses. An earlier investigation in monkeys by Van Horn et al. (2013) found convergence cells in the rostral superior colliculus that responded to slow vergences dynamics only, and they proposed that these were involved in the slow vergence component. Hence, Rucker et al. (2019) then proposed that the rostral superior colliculus abnormality found in their patient could be due to loss of neural integrator function, which acts to complete and sustain the response.

The major limitation of this interesting and provocative clinical study was its single case report nature. Further work is needed to confirm these findings in other patients manifesting similar abnormal vergence responses and visual symptoms, and rostral superior colliculus damage, with objective documentation. Also, the dynamic responses were not analyzed quantitatively.

STUDY 5: A recent investigation by Alvarez et al. (2021) was the *first* (pilot) study to assess vergence dynamics in the pediatric population (aged 11–17 years). The goal was to determine if those with convergence insufficiency (CI) only (n = 10) differed from those with CI *and* persistent post-concussion symptoms (i.e., at least one month post-injury)/mTBI (n = 15), all compared to a binocularly-normal control group (n = 11). The general design was similar to that described in Study 3. However, now the ISCAN DK2 eye movement system was embedded into an Oculus DK2 head-mounted display (Facebook Inc, Menlo Park, CA, USA). Symmetric convergence and divergence stimuli were placed at stimulus demands of 6 and 10 degs. for an overall stimulus change of 4 degs, with temporal randomization to minimize prediction. The stimuli consisted of one-degree X's having a luminance of 5 cd/m-squared, with a background of 0.8 cd/m-squared, thus a very dim overall stimulus condition in the reduced cue environment; no other visual stimuli were present.

The ensemble responses are presented in Fig. 4 in the three groups for the first 1.5 secs of the 4 s recording period. Interestingly, in all groups, the mean residual vergence error was large; hardly any in the normal group appeared to acquire the target, while none of those with CI did. Based on the last 0.5 secs. of the 4 sec. recordings, the mean final amplitude errors were 0.7, 2.4, and 3.0 degs., respectively, in the normals, those with CI only, and those with CI and concussion. In addition, while the mean convergence peak velocities found in the two CI groups were much lower than in the normal group, they were appropriate given their smaller response amplitudes; hence, they were normal and as expected per the main sequence neurological relation (Hung et al., 1994). This finding is in contrast to that found in studies 1 and 2 in adults with chronic mTBI, in which the amplitudes were accurate but the peak velocities were reduced and abnormal per the main sequence relation. This major difference warrants further investigation.

There are two possibilities that could explain these pediatric versus adult differences. First, in their normal pediatric group, the large, steady-state vergence errors could be due to age-related developmental aspects. However, these subjects were carefully tested both medically and optometrically, and they were deemed to have "normal binocular vision", hence presence of expected and frequent intermittent diplopia with such large errors (0.7 degs.) under more naturalistic conditions would be unlikely. The second more likely possibility is related to the reduced cue environment and the very low test target luminances (Chen et al., 2021). If the target distances were misperceived depth-wise for the given disparity, then the initial response component (i.e., the pre-programmed, open-loop aspect) would likewise be adversely affected and reflect this perceptual problem, thus manifesting an effectively reduced vergence controller gain. This possibility warrants further testing of the vergence/apparent distance relation (von Hofsten, 1976) in the two CI populations under a similar reduced cue environment.

There were four potential study limitations. First, sample size was small. Second, the last 2.5 secs. of the 4 sec. recordings were not presented nor described in detail with respect to the dynamics, thus one cannot accurately determine the attributes of the overall slow vergence component, if present, and furthermore how the children respond during this period: was diplopia reported, visual confusion, etc., as three children were initially removed from the study as they had difficulty responding. Fourth, brain imaging was not performed.

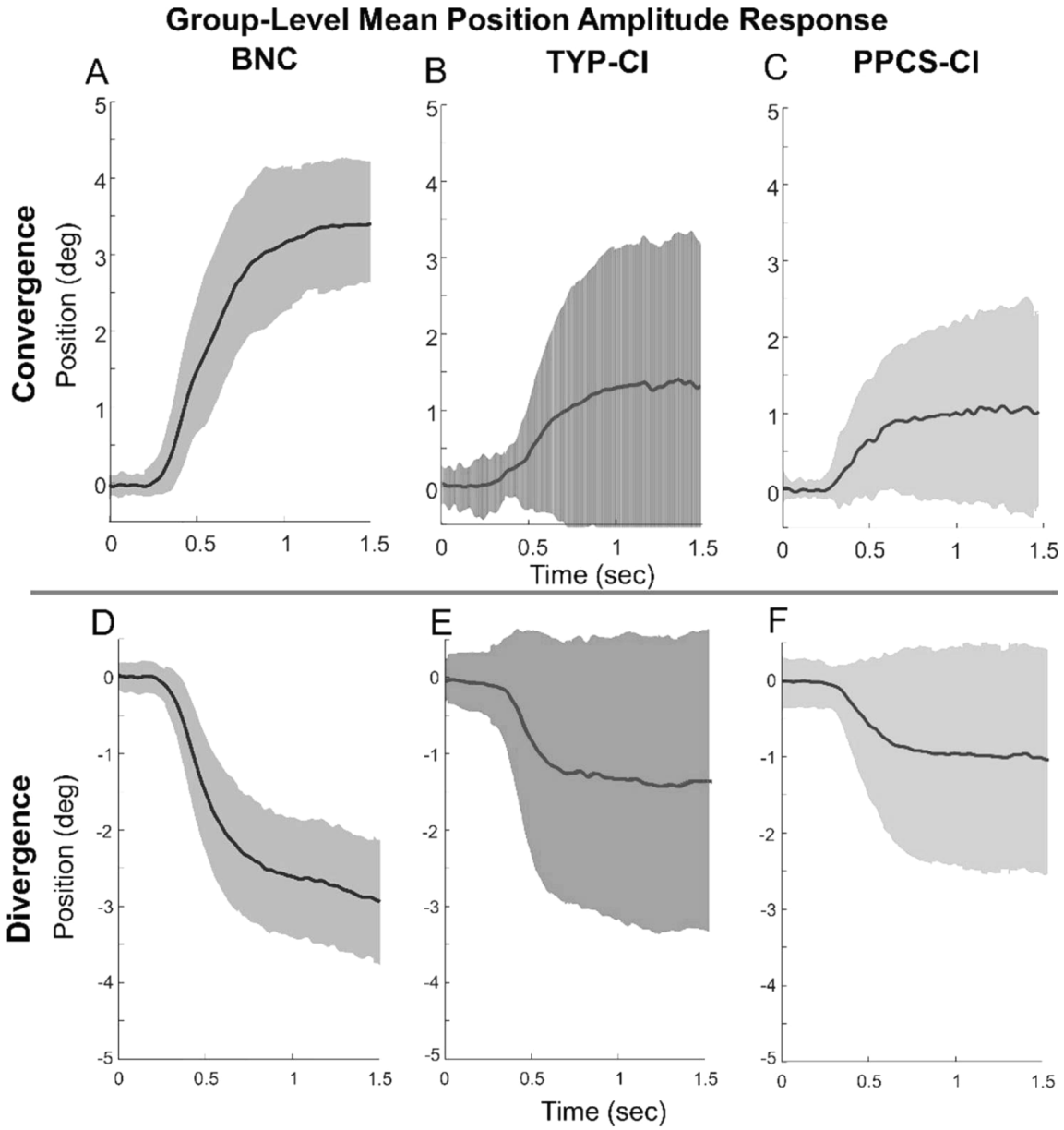

Fig. 4. Group-level mean +/- 1 standard deviation (SD) position trace in degrees as a function of time (seconds) (solid line) and +/- SD (shaded area) for the following groups: binocularly-normal control (BNC) convergence (2A) and divergence (2D), typical CI (Typ-CI) convergence (2B) and divergence (2E), and persistent post-concussion symptoms (PPCS) with CI for convergence (2C) and divergence (2F). (Adapted with permission, Alvarez et al., 2021).

5. Laboratory investigations using objective recording of accommodative dynamics in mTBI

There have been two primary studies using objective recording techniques and detailed quantitative analysis in the area. These will be discussed including the major findings, basic and clinical implications, and potential study limitations. Each study provides new and important insights and dimensions into understanding the dysfunctional accommodative system in those with visually- symptomatic mTBI.

STUDY 1: The first investigation was performed by Green et al. (2010). A primary goal was to assess dynamic accommodative characteristics in mTBI. This was the *first* study of its kind. There were 12 individuals (aged 18–40 years, mean = 31 years) with medically diagnosed, chronic mTBI, and 10 age-matched, visually-normal controls (aged 22–35 years, mean = 27 years), with both non-presbyopic groups having similar gender ratios. All received a comprehensive vision examination prior to testing and had 20/25 or better distance and near visual acuity with refractive correction. None had constant strabismus. All with mTBI reported typical near vision problems (e.g., intermittent blur, eyestrain). Increasing and decreasing accommodative responses were assessed objectively using the WAM-5500, infrared, open-field autorefractor (Grand Seiko; Hiroshima, Japan) under monocular viewing conditions; the non-tested eye was fully occluded. The autorefractor has a 5 Hz sampling rate in its dynamic mode, which satisfies the Nyquist criterion. Resolution as reported by the manufacturer is 0.01 D. Targets were positioned at 50 cm (2D) and 25 cm (4D) along the line-of-sight of the right eye and were comprised of high-contrast Snellen letters (20/30–20/60), with a luminance of 36 cd/m-squared. Room illumination was subdued (2.8 lx). There were ~16 changes in focus between the two targets over the 120 s test period as verbally directed by the experimenter to minimize prediction effects. Responses were accurately fit with a decreasing exponential.

The individual dynamic responses were interesting. Typical responses are presented in Fig. 5 for a control subject, and also for an

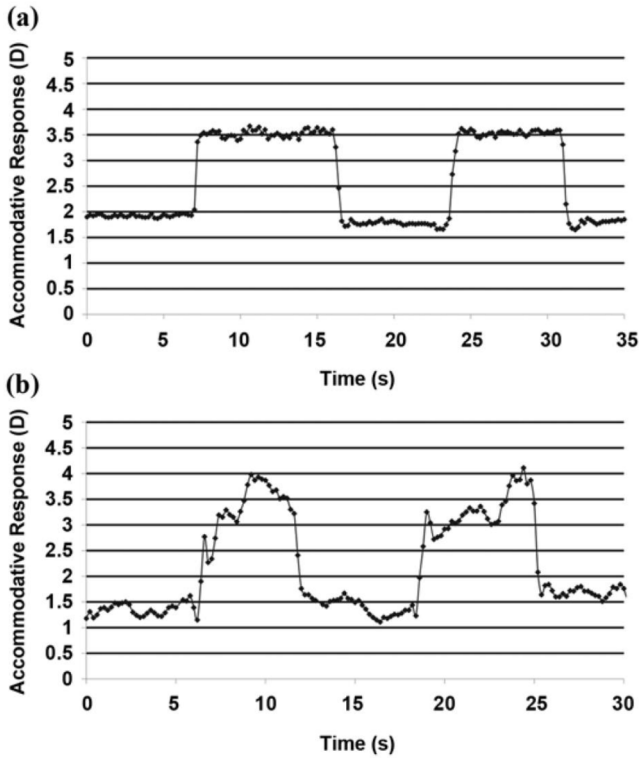

Fig. 5. Dynamic accommodative responses to near stimuli (2D and 4D) as a function of time in a (a) control subject and (b) in a subject with mild traumatic brain injury manifesting significant response abnormalities. Monocular viewing with the right eye. Expanded time scale. (Adapted with permission, Green et al., 2010).

individual with mTBI who exhibited highly abnormal, slowed responses profiles. In the latter case, markedly increased variability was found for both the transient, dynamic trajectories and the subsequent steady-state levels, especially for near target acquisition. Fig. 6 presents typical dynamic responses for both increasing and decreasing accommodation with an expanded time scale in a control subject, and in an individual with mTBI exhibiting markedly slowed responses, being approximately 2–3 times slower/longer as compared to the normal subject.

The group data mirrored the individual responses, which ranged from mild to severe abnormalities. They were slowed and more variable throughout the time course in all those with mTBI, but on average attained the proper, final mean amplitude (i.e., steady-state level). First, peak velocities for both increasing and decreasing accommodation were ~25–45% reduced (i.e., slower) in the mTBI cohort versus the normal group. Second, the times constants and steady-state variability levels were increased by similar amounts (~25–45%) in those with mTBI versus the controls. These dynamic abnormalities are likely to have adverse impact on one's quality of life (QOL), both vocationally and avocationally, especially for near tasks such as sustained reading.

The results demonstrate the considerable and pervasive abnormalities in accommodative dynamics in adults with chronic mTBI, similar to that found for vergence, as described earlier. The findings suggest abnormal motoneuronal control, that is deficits in the postulated midbrain pulse-step controller, similar to that speculated earlier for vergence. The pulse height might be too small, thus resulting in a slowed dynamic trajectory. The step, on average, appears to be the appropriate size but with either increased gain instability and/or increased neural noise, thus resulting in increased steady-state, response variability but with overall mean accuracy. Any visual rehabilitation should target both the slow and fast accommodative components to attain response normalcy.

There were four potential study limitations. First, sample size was relatively small. Second, while the autorefractor's sampling rate was sufficient, a higher rate would have better detected and defined any small, dynamic variations; in addition, it would have provided a better estimate of steady-state variability. Third, latency was not assessed due to technical limitations. Fourth, brain imaging was not performed to determine the site(s) of neurological abnormality.

STUDY 2: The second investigation was performed by Thiagarajan and Ciuffreda (2014b). A primary goal was to assess accommodative dynamics in those with mTBI before and after a clinical visual intervention. It was the *first* clinical trial to record and quantify the effects of conventional, neuro-optometric vision therapy on the abnormal accommodative dynamics found in younger adults with chronic mTBI (Green et al., 2010). There was 12 individuals (ages 23–33 years, mean = 29 years) with medically-diagnosed, chronic, mTBI, comprised of 4 males and 8 females. Subjects had to be less than 40 years of age (i.e., non-presbyopic), so that their linear accommodative range was within the test stimuli dioptric levels (2 and 4D).

The overall instrumentation and stimuli were as described in Study 1 (Green et al., 2010), whereas the overall cross-over, interventional design was, in general, as described in the prior section on vergence (Study 2; Thiagarajan and Ciuffreda, 2013). However, now the subjects received a total of 3 h of accommodative therapy over the 6 weeks involving both the fast and slow system components. The dioptric training stimuli were produced by changes in spherical lens and/or target distance, and these levels were increased as performance improved. There was also a placebo arm (i.e., sham), which all subjects believed to be a true therapeutic phase.

The results were interesting. First, the baseline accommodative dynamics for the 2 and 4D test stimuli were slowed and more variable for both increasing and decreasing accommodation, thus confirming the earlier findings of Green et al. (2010). Second, and most importantly, all group dynamics that were abnormal at baseline (i.e., peak velocity and time constant for increasing and decreasing accommodation) significantly improved by 30–40% following the therapy (Figs. 7 and 8) but did not normalize. Steady-state response level, steady-state variability, and response amplitude were all normal prior to the therapy (i.e., at baseline testing), and hence remained the same following the intervention. Lastly, there were no significant changes in dynamics for the placebo group following the sham phase.

Dynamic responses are presented in Fig. 9 for a typical subject with mTBI before and after the therapy for both increasing and decreasing accommodation (2 and 4D test stimuli). The faster overall response time course with less dynamic trajectory variability is evident following the therapy.

The results demonstrate the considerable and pervasive baseline abnormalities in accommodation in adults with chronic mTBI that were significantly improved following the brief therapeutic time course (i.e., 3 h distributed over 6 weeks). The findings suggest a considerable degree of brain neuroplasticity, as well as rapid perceptual and motor learning effects (Hebb, 1949), even in adults with a chronically-damaged brain, following the therapy, and as earlier described for vergence (Study 2, Thiagarajan and Ciuffreda, 2013). Moreover, using the validated CISS visual symptom survey (Rouse et al., 2009), the overall score reduced significantly by 30%, thus indicating a reduction in baseline visual symptoms at near, although it did not normalize.

There were six potential study limitations. First, sample size was small but appropriate per the power analysis calculation. Second, while the autorefractor's sampling rate (5 Hz) was adequate per the Nyquist criterion, a higher rate might have better detected and defined any small, dynamic variations. Third, latency was not assessed due to technical limitations. Fourth, brain imaging was not performed to detect areas of initial abnormality and the correlated changes following therapy. Fifth, the therapeutic "dosage" was very small due to both experimental design and practical limitations; this is typically 10 or more hours in the conventional clinical setting. They should be extended to match the clinical domain in future studies to determine if objectively-

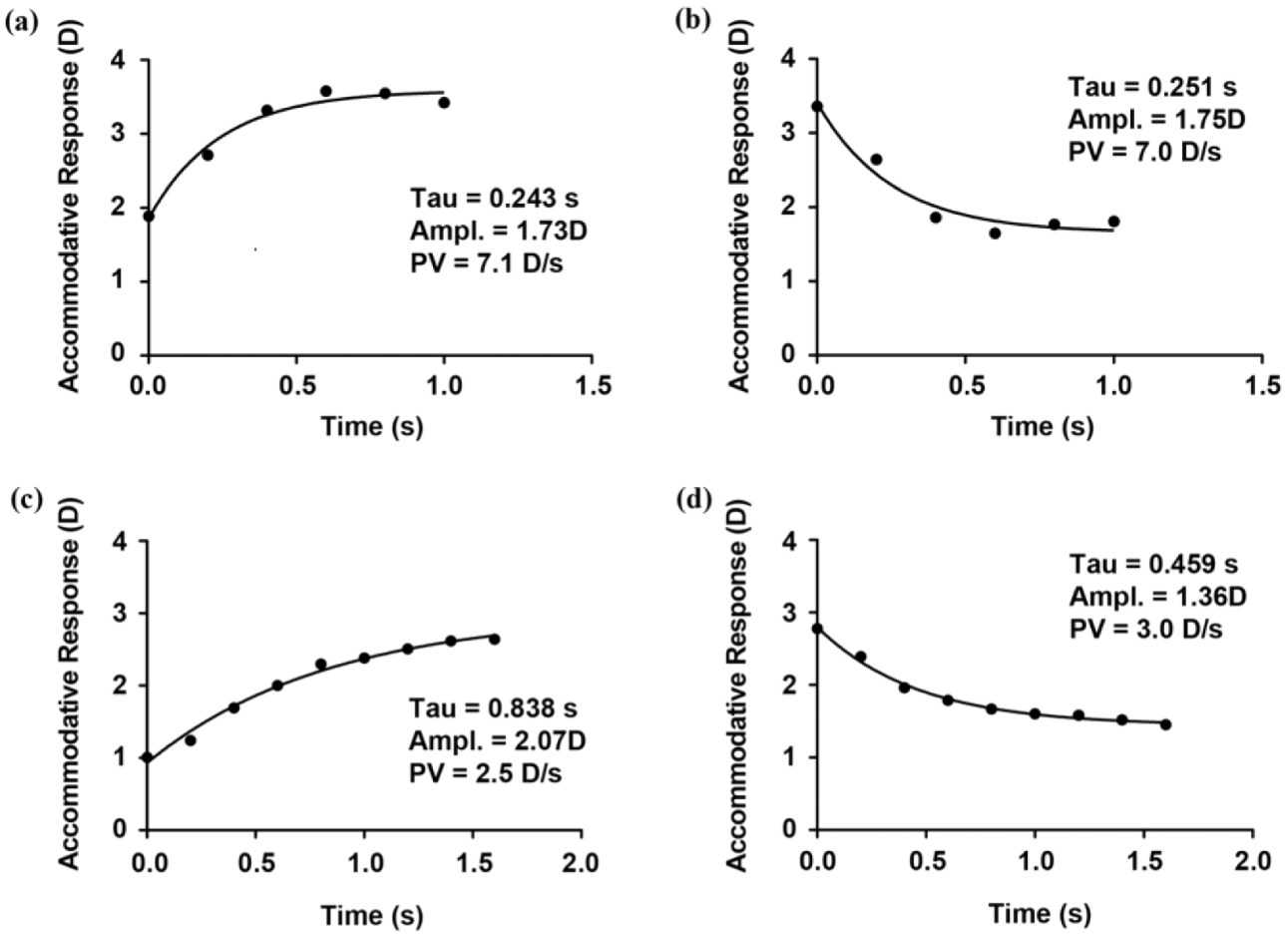

Fig. 6. Exponential fit to raw data (accommodative response as function of time) for a typical control subject for (a) increasing and (b) decreasing accommodation and an mTBI subject manifesting more severe dynamic abnormalities for both (c) increasing and (d) decreasing accommodation. Ampl. = response amplitude, PV = peak velocity, Tau = time constant. (Adapted with permission, Green et al., 2010).

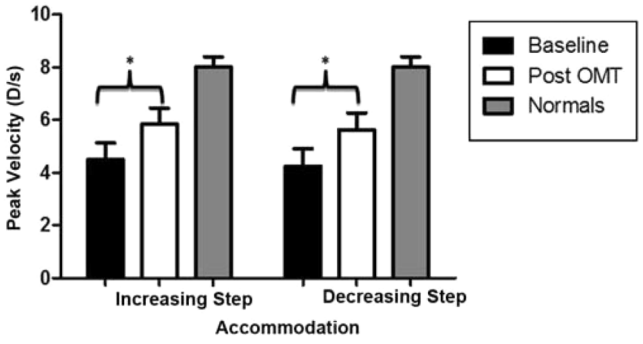

Fig. 7. Group mean peak velocity of accommodation before (baseline) and after oculomotor training (post OMT) in mild traumatic brain injury in comparison with normal. Error bars indicate + 1 standard error of mean. *Significantly increased from baseline. D = diopter. (Adapted with permission, Thiagarajan & Ciuffreda, 2014).

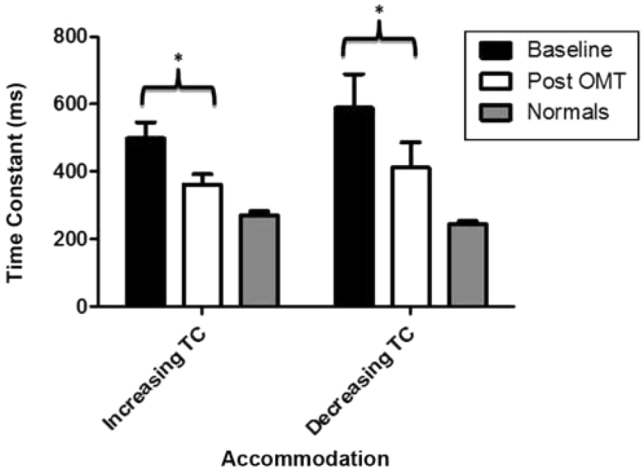

Fig. 8. Group mean time constant (TC) for accommodation before (baseline) and after oculomotor training (post OMT) in mild traumatic brain injury in comparison with normal. Error bars indicate + 1 standard error of mean. *Significantly decreased from baseline. (Adapted with permission, Thiagarajan & Ciuffreda, 2014).

based, dynamic response normalization is attained. Sixth, there was no follow-up to assess for persistence of the dynamic improvements, and this should be done periodically over at least a one-year period following termination of therapy.

6. Discussion

A review of the important findings from the key studies on vergence and on accommodative dynamics in individuals with mTBI provides unique and critical insights into this area, as well as thought for future research endeavors. Most of the dynamic parameters were abnormal at

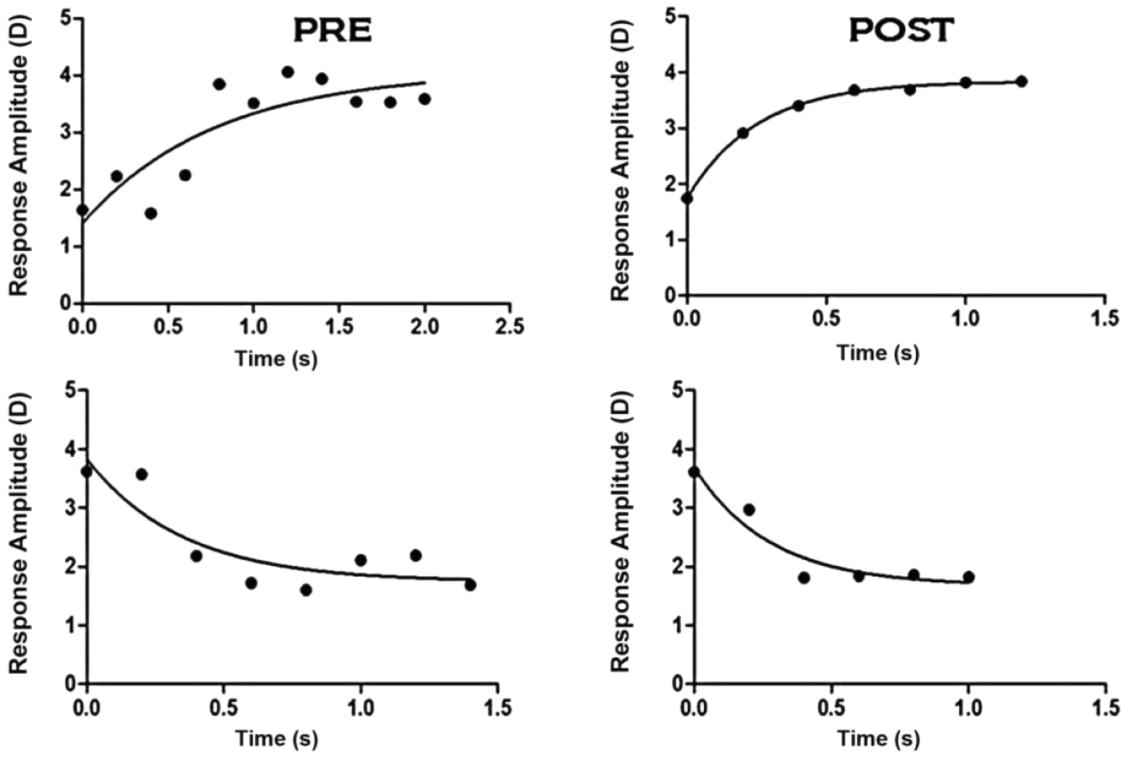

Fig. 9. Accommodative dynamic trajectory as function of time. Exponential fit of two-dimensional step accommodative dynamic trajectory before (left column) and after (right column) oculomotor training for increasing (top row) and decreasing (bottom row) step accommodation in typical subject with mild traumatic brain injury. D = diopter. (Adapted with permission, Thiagarajan & Ciuffreda, 2014).

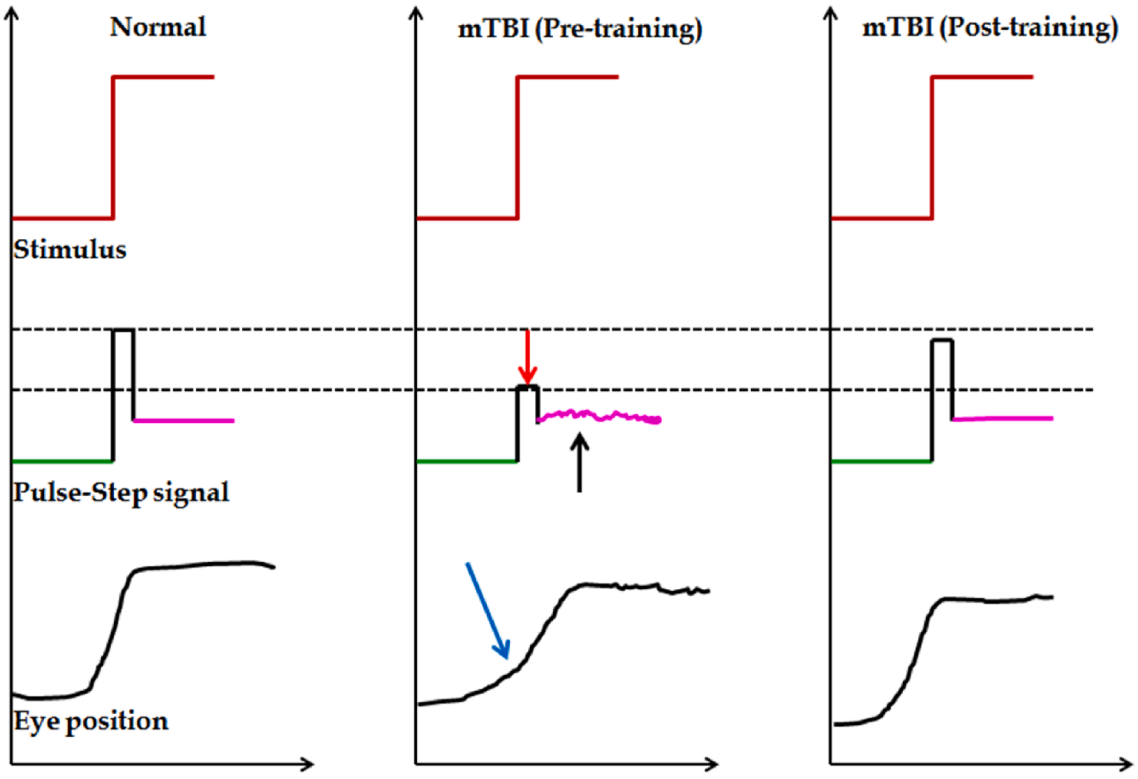

Fig. 10. Postulated neural pulse-step controller for vergence (and also accommodation) in a normal subject and in one with mTBI. Schematic representation of proposed condition and resultant therapy effects, all as a function of relative time. Arrows show defective pulse (down arrow) and step (up arrow) components in mTBI pre-training. Post-training, the pulse height increases, and the step variability decreases. The pulse height is exaggerated relative to the step for purposes of clarity. Diagonal arrow show slowed dynamic trajectory pre-training (Adapted with permission, Thiagarajan, 2012).

baseline. For example, peak convergence and accommodative velocities were consistently and considerably reduced. This is consistent with the biomechanical notion of the adverse effects of rapid neck flexure on the vulnerable midbrain in the typical brain injury (i.e., coup-contrecoup) (Rucker et al., 2019). Thus, these parameters, and others, are likely to be a potential, high-yield, non-invasive, vision-based biomarkers for mTBI/concussion (Ciuffreda et al., 2014).

The rehabilitative findings reveal the remarkable ability of the human to learn/relearn basic oculomotor maneuvers to approach time-optimality, even in the damaged adult brain in the chronic stage, that is years after the insult and beyond the period of any natural recovery. Furthermore, it is remarkable that as little as 3 h of specific, programmed training distributed over several weeks can have considerable positive impact on the system's dynamic motor responsivity, as well as on related visual performance measures such as reading (Thiagarajan et al., 2014) which requires the vergence angle to remain relatively constant (i.e., within foveal Panum's areas) during the sequential, repetitive fixational pauses for extended periods of time, with similar arguments for accommodation. And, with additional vergence training time, some even attained normalcy. These findings represent a powerful demonstration of visual system plasticity under extremely adverse biological circumstances in humans.

Over the past several years, the pulse-step signal has been proposed to be the underlying neurological controller for both the vergence and accommodative systems in normals, based on laboratory and modelling studies, as described earlier. Similarly, pulse-step control has also been proposed, or at least implied, in the context of those with mTBI, and assumed to represent a logical extension, as also described earlier. Furthermore, pulse-step control has been modelled in a global, non-quantitative, conceptual model in mTBI (Thiagarajan, 2012) (Fig. 10). Pre-therapy, it has been conceptualized as a pulse-step with reduced height and slightly increased step variability. Post-therapy, it has been proposed that the pulse height increases, and the step variability decreases. Thus, the response dynamics are improved with treatment. While the pulse-step assumption is likely correct in normals, it may or may not be the case in mTBI: the approach may be too simplistic. First, in some of the vergence studies, there was a very wide range of dynamic response profiles to the convergence step inputs prior to any therapeutic intervention. This was especially true in Experiment 5 (Alvarez et al., 2021) (their Fig. 2). The variability was approximately twice as large as found in their normal cohort. Moreover, some of the responses were extremely small, with all being much less than the vergence stimulus demand over the 3-second period shown. Second, in Experiment 3 (Scheiman et al., 2017) (their Fig. 4A), the 3-second response appears to be a very slow ramp with a large, residual positional error, as described earlier, again prior to any therapeutic intervention, that is representing their baseline status. Thus, one might speculate that this very abnormal response could be controlled by a single, pulse-LESS step, or even a series of step-ONLY neural signals based on the continuous nature (i.e., closed-loop) of the slow vergence component. Third, and related to the post-therapeutic findings, the simple proposal that pulse height is increased to improve peak velocity and the correlated motor response dynamic profile may not be true in all cases: there might not be a pulse to modify. Furthermore, over the therapeutic time period, as well as during any prior degree of natural recovery/motor adaptation, the resultant neural signals may be different or more complicated. For example, in the slow ramp response found, there would be no apparent pulse aspect to modify with therapy. Moreover, because a response appears to be improved following an intervention, it does not necessarily demand that the underlying neural signal might also be, say a relatively normal pulse-step: it could be a different/more complicated, adaptive signal developed during the early pre-therapy period, or even in response to the subsequent therapy. Thus, there are many likely unknowns. Hence, in addition to the need for careful modelling studies in the future, it would be imperative to record these neural signals directly using electromyography (EMG) both before and after any visual intervention.

Lastly, there are several possible future directions for research that would yield additional insight into the area. These include:

Modelling of the vergence and accommodative systems should be performed, including both dynamic and static aspects for completeness. This would allow for "dry dissection" of the neural pathways and their components. It could involve both traditional "black box", bioengineering approaches (Schor & Ciuffreda, 1983), as well as more "physiologically"-based ones using MATLAB and incorporating basic neural components such as the pulse generator (Hung, 1998). This would allow for better conceptualization of the site(s) of brain injury as suggested by the oculomotor and brain imaging laboratory studies, as well as for determining the relative impact on overall responsivity, accuracy, and timing aspects (e.g., processing delays) using sensitivity analysis (Hung and Ciuffreda, 1994).

More comprehensive clinical trials involving the vergence and accommodative systems should be performed. This should include objective recording of the responses, with correlated brain imaging and visual performance measures (e.g., reading) before and after a therapeutic intervention (e.g., vision therapy, near vision lenses, vergence prisms). In addition, it might include assessing "dose" effects (e.g., 3 hrs versus 6 h versus 9 h total) to determine the most efficacious treatment protocol, as well as long-term follow-up (e.g., 1–3 years) for determining persistence effects. It should also expanded to include those with moderate and severe TBI, which remain underserved (Ciuffreda, Tannen & Suter, 2020).

Training should include both step and ramp stimulation to "rehabilitate" both the fast and slow components (Szymanowicz et al., 2012; Thiagarajan and Ciuffreda, 2013; 2014).

Development of simple, rapid, portable, objective, quantitative, automated test systems to assess for dynamic vergence deficits in a range of environments (e.g., the sports sidelines, sports medicine physician's office) and in a wider range of populations (e.g., young children, those with severe TBI done at bedside). For example, it has been proposed to incorporate vergence test stimuli and objective recording systems into virtual/augmented reality devices with automated analysis of key parameters such as convergence peak velocity (Ciuffreda, Ludlam & Yadav, 2018), and which has recently been reported (Alvarez et al., 2021). A similar argument can be made for the accommodative system.

7. Conclusions

These investigations represent "pioneering" efforts in the evolving field of oculomotor-based, visual dysfunctions and their remediation in adults with chronic mTBI. First, they characterized many of the dynamic deficits of the key vergence and accommodative parameters commonly found in this population. Second, they revealed the remarkable degree of underlying neural plasticity, even in the damaged adult brain in the late chronic phase of mTBI. And, third, they set the groundwork for future studies incorporating both behavioral and brain-related measures employing objective techniques before and after a visual intervention.

CRediT authorship contribution statement

Kenneth J. Ciuffreda: Conceptualization, Writing – review & editing. **Preethi Thiagarajan:** Conceptualization, Writing – review & editing.

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