Feasibility of using normobaric hypoxic stress in mTBI research

Studies of mild traumatic brain injury (mTBI) recovery generally assess patients in unstressed conditions that permit compensation for impairments through increased effort expenditure. This possibility may explain why a subgroup of individuals report persistent mTBI symptoms yet perform normally on objective assessment. Accordingly, the development and utilization of stress paradigms may be effective for enhancing the sensitivity of mTBI assessment. Previous studies, discussed here, indirectly but plausibly support the use of normobaric hypoxia as a stressor in uncovering latent mTBI symptoms due to the overlapping symptomatology induced by both normobaric hypoxia and mTBI. Limited studies by our group and others further support this plausibility through proof-of-concept demonstrations that hypoxia reversibly induces disproportionately severe impairments of oculomotor, pupillometric, cognitive and autonomic function in mTBI individuals.

Keywords: concussion • mTBI assessment • hypoxia • stress • mild traumatic brain injury

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Recovery from the acute symptoms of mild traumatic brain injury (mTBI), alternatively termed concussion, typically occurs within 7–10 days postinjury, though the WHO and others have stated that symptoms may persist up to 90-day postinjury [1–5]. It should be noted that these estimates of mTBI symptom duration are based on postinjury assessments performed while patients are in unstressed settings such as exam rooms and healthcare offices [6]. Such low-stress environments may permit some patients to compensate for symptoms by temporarily increasing effort expenditure in order to increase performance to levels indistinguishable from that of healthy individuals. In other words, clinical and research examination under low-stress conditions may be insufficient to cross the threshold for observable or measurable symptoms in some mTBI individuals. This possibility may be the reason why a subgroup of

mTBI individuals report persistent symptoms and chronic impairment despite being asymptomatic on clinical examinations [7,8]. Stress paradigms that challenge the patient and require ‘extra effort’ may be an effective adjunct for uncovering latent or hidden mTBI symptoms.

The present paper discusses the scientific rationale for studying mTBI using an approach that combines multimodal assessment with hypoxic stress, specifically normobaric hypoxia (NH). As will be discussed below, hypoxic stress, including NH, provokes reversible deficits in cognitive, oculomotor, pupillometric and autonomic nervous system (ANS) functions in healthy individuals. Moreover, preliminary studies by our group and others have shown that hypoxia has a disproportionately negative impact upon concussed individuals. As such, NH may increase the sensitivity of multi-

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modal mTBI symptom assessment by disproportionately increasing deficits in mTBI individuals in a safe and reversible manner. This disproportionate effect may be due to the fact that, at rest, mTBI individuals are closer to their maximum capabilities (i.e., the threshold above which additional cognitive effort is no longer remedial in maintaining performance) than non-concussed individuals and therefore are more vulnerable to resource depletion when stressed. Thus, NH may be a useful method for driving mTBI individuals past compensatory levels of normal performance into a state of temporary, reversible, but observable mTBI-related symptoms. It should be noted, however, that the emphasis of the present paper is on describing the scientific foundation for employing this combinatory form of assessment. At present, there are no published studies using the full combination of proposed modalities, such that our review is limited to presentation of the scientific foundation underlying each of the modalities we propose to combine. In addition, studies that actually have used hypoxic stress in mTBI research are limited to those by our group and others, as discussed below, such that this small body of research should be regarded more as 'proof-of-concept' rather than full-fledged scientific support or presently translatable to clinical applications.

An additional distinction that must be made is the fundamental differences between hypobaric hypoxia (HH) and NH discussed in the current paper. In general, hypoxia is defined as an inspired partial pressure of oxygen (PI_{O_2}) less than 150 mmHg and may be due to a reduction in barometric pressure (P_B), a reduction in the inspired fraction of oxygen (FI_{O_2}), or any combination of either [9]. While traditionally it was thought that the only contributing factor to the physiological responses to hypoxia was PI_{O_2} , there has been an increasing debate on the differing contributions of P_B and FI_{O_2} to these physiological responses as well and, as such, whether HH and NH can be used interchangeably [9–12]. Furthermore, the short- and long-term effects of iatrogenic conditions of both HH and NH would be markedly different from chronic, intermittent hypoxia due to medical conditions such as chronic obstructive pulmonary disease and sleep apnea. To this extent, the important distinction for the present paper is not the degree of equivalence between hypobaric and normobaric hypoxic conditions, nor between iatrogenic and chronic, intermittent hypoxic conditions, but rather the suitability of hypoxic stress to evoke some degree of disproportionate physiological or cognitive response in individuals with mTBI. Therefore, the current paper will consider both HH and NH conditions in the parallel symptomatology between mTBI and hypoxia, with the understanding

that future investigations and clinical applications will need to confirm symptomatology of an assessment modality under defined NH conditions given its superiority over HH conditions in terms of ease of use, reproducibility and safety.

Parallel symptomatology of mTBI & hypoxia Cognitive functions

Immediate, acute cognitive symptoms of mTBI are well-recognized and include decreased performance on neurocognitive tests with impairments in attention, concentration, information processing speed, anticipation, planning, executive functioning and memory, including working and verbal memory [13–18]. To a lesser extent, in some mTBI individuals, particularly those with a history of multiple mTBIs, long-term, persistent cognitive deficits also have been identified, including impairments in attention, information processing and memory as well as impairments in cognitive flexibility, problem-solving and cognitive control [19–21]. Similarly, regarding NH, it is well known that cognitive functioning, including working memory, is susceptible to NH-induced deficits and that these deficits are easily reversible when returned to normoxia [11,22].

Oculomotor & pupillometric functions

Oculomotor functions, as well as functional movement of the pupil, are widely acknowledged to have great potential as behaviorally based objective biomarkers for mTBI [23–29]. The neural control of eye movements depends critically on the complex coordination and timing of neural circuitry distributed widely throughout multiple areas of the brain, including the frontal lobe, basal ganglia, superior colliculus and the cerebellum [30–33]. Specific deficits in oculomotor functions can be classed as deficits in smooth pursuit eye movements (SPEM), saccades and fixation-related behaviors. When performing circular smooth pursuit-tracking tasks, mTBI-related deficits in SPEM include decreased target prediction, increased eye position error, increased variability of eye position error [32,33], higher range inaccuracy in visual tracking as measured by variability of gaze position error relative to the target [31,34], smaller primary saccades, larger saccadic position errors, smaller saccadic amplitudes, slower predicted peak velocities, slower peak accelerations and abnormal pursuit velocities [35]. mTBI-related deficits in saccadic eye movements include significantly larger number of saccades but with significantly less precisely controlled end points [35–37]. In addition, mTBI impacts the response of the pupil in a number of ways. The pupil response latency and amplitude of constriction [35], as well as pupillary light reflex, a dynamic, time-dependent waveform with a characteristic time

course that identifies maximum pupil diameter, minimum pupil diameter, percent pupil constriction, constriction latency, 75% recovery time, average constriction velocity, maximum constriction recovery, and dilation velocity [24,38,39] have been demonstrated to be affected by mTBI.

The sensitivity of the visual and oculomotor systems to hypoxia is well established. Visual functions sensitive to hypoxia include light and dark adaptation, visual acuity, central and peripheral visual field perception, color vision, latency and intensity of negative after-images and flicker fusion frequency, whereas oculomotor functions sensitive to hypoxia include extraocular muscle functioning, accommodation, convergence and coordination [40,41]. Functional oculomotor deficits under hypoxia include deficits in saccadic [42,43] and SPEM [44]. In addition, there is the literature demonstrating the effects of altitude and hypoxia on the pupil, with consistent findings being a slight decrease in pupil diameter as well as effects in the monocular/direct and binocular/conceptual pupillary light reflex [40,42,43,45–47].

ANS regulatory functions

Multiple ANS functions also are known to be susceptible to mTBI-related dysregulation. For instance, Len and colleagues have consistently shown that mTBI reduces cerebrovascular reactivity [48,49] and mTBI individuals have shown higher heart rate, decreased heart rate variability and reduced skin conductance in comparison to healthy individuals [50–56]. Moreover, there are strong reasons to expect that these measures of ANS function are sensitive to hypoxia, as the literature indicates the existence of differences in pulse oximetry, aspects of cerebrovascular regulatory responses, heart rate, electrodermal activity and the cardiovascular response [11,57,58].

Using hypoxia in mTBI assessment

While mTBI and hypoxia independently elicit deficits in cognitive, oculomotor, pupillometric and ANS functions, the effects of hypoxia on individuals with mTBI have received less study. The idea that mTBI and hypoxic stress may have combinational, and thereby disproportionate, effects were formulated from observations made during a 1980 study of a group of ten university students who had experienced ‘minor head injury’ 1–3 years prior to the study [59]. At the time of the study, these students were asymptomatic and performing comparably to preinjury levels. These students, along with a control group of ten students matched on the basis of age, gender and academic performance were exposed for 30 min in a low-pressure chamber to an altitude challenge of 3800 m (about 12,500 ft.) above mean sea level

(MSL). None of the students in the experimental group were symptomatic at MSL, however, at altitude there were clear deficits in short-term memory and judgment on a signal detection task, effects that manifested within 10 min of altitude exposure. These effects were reversible, disappearing when the students were returned to MSL. The stressor in this study was HH, a less practical and more risky procedure compared with the NH employed in more recent studies, an important point elaborated further below.

The hypothesis that a physiologic stress challenge, such as NH, can uncover latent, hidden or subclinical symptoms of concussion was corroborated by the current group during an experiment evaluating the simulated flight performance of highly skilled, active duty military instructor pilots undergoing NH exposure approximating 18,000 ft. above MSL [60]. Under the control condition of breathing MSL air, the flight performance of all pilots was consistent with their high-level expertise. However, when the pilots were breathing a NH simulation approximating 18,000 ft. above MSL, one pilot not only lost control of the aircraft but did not realize that fact. A subsequent review of the pilot’s medical record showed that several years earlier the pilot had sustained a mTBI while ejecting from a high-performance aircraft. A follow-up study [61] specifically evaluated NH as a potential challenge modality to assess the latent effects of mTBI in asymptomatic individuals by examining short-term visual memory in group of 36 civilian volunteers with a history of concussion and an equal number of civilian control volunteers without a history of concussion. These two groups of volunteers were matched on the basis of age, gender, BMI, height, weight, resting blood pressures, pulse rate and respiration rate. While there was no difference between the two groups at MSL, short-term visual memory showed significantly greater impairment in the mTBI group at 12,000 ft. above MSL, a difference which disappeared when the subjects returned to MSL.

Hypoxia & cerebral resource depletion

Although the immediate, acute symptoms of mTBI are well recognized, neurocognitive and neuropsychological difficulties attributable to mTBI within the post-acute phase have not been as readily characterized [62–64] despite consistent reporting of symptoms [7,8,65,66]. This may be due to the lack of identifiable abnormalities on standard neurological imaging [66–70] and/or the potential for both psychological and physiological etiologies of subjective symptoms [62–66,71,72]. Furthermore, as suggested by Marshall and Ruff, conventional assessment of mTBI may lack sensitivity because patients can compensate for difficulties by expending greater cerebral effort to achieve normal performance:

'The problem with testing performance in a laboratory setting is that the individual gears up or increases the level of intellectual energy expenditure to function' [73]. In essence, apparently asymptomatic mTBI patients may be applying greater cerebral effort and resources when being evaluated or tested. While it may be argued that control subjects could be doing exactly the same thing, the mTBI subjects, who would have smaller reserve capabilities, would be operating closer to their maximum capabilities and thus would be more vulnerable to resource depletion when stressed, particularly during tasks dependent on processing speed, working memory and executive function [66,74].

Indeed, Ozen and Fernandes reported that neuropsychological tasks did not differentiate between mTBI and healthy individuals, as both groups displayed similar accuracy in a working memory task. However, mTBI individuals took slightly longer to complete a working memory task and reported higher states of anxiety. This observation suggests that individuals with mTBI history adopt a strategy of decreased speed in order to maintain preinjury levels of accuracy [75]. Similarly, Maruta *et al.* also found that mTBI individuals were able to maintain accuracy on reaction time-based neurocognitive tasks, but at the expense of reduced efficiency and increased fatigue [64].

Satz's Brain Reserve Capacity (BRC) model may serve as an explanatory construct for the present findings. The model proposes that individuals with different amounts of BRC, also called cognitive reserve, may have different Functional Impairment Thresholds (FIT). Concussed individuals with BRC above the FIT evidence no discernable performance deficit, but those with BRC below the FIT do show a deficit [76]. Environmental and other challenges can consume portions of the BRC, thereby facilitating the emergence of measurable cognitive [77] or physiological [55,78] impairments in mTBI individuals. Satz noted that this concept has long been used in neurotoxicology to uncover otherwise latent or subthreshold toxicity through the use of special drug challenges. The BRC model has been used to explain why individuals commonly may be symptom-free yet still have significant neuroanatomical abnormality, including Lewy bodies, infarcts, neurofibrillary tangles, neuritic plaques and amyloid- β plaques [76,79–81].

Recent studies are consistent with the BRC model of mTBI. fMRI and EEG studies have shown abnormalities in mTBI athletes who were deemed medically and neuropsychologically fully recovered and who had been cleared to return to contact sports. These abnormalities included alterations of interhemispheric connectivity and reduction in neural activity in the temporal, parietal and occipital regions [82]. Several studies show that when mTBI and healthy subjects are equated for

cognitive performance, mTBI individuals show abnormalities, in particular abnormalities related to using increased cerebral resources while maintaining 'normal' cognitive performance [83–85]. Similar results were found by Jantzen *et al.*, who obtained fMRI baselines on a group of athletes and then reassessed concussed athletes a week after injury. Concussed athletes showed postinjury cognitive performance similar to their pre-injury baselines, but there were 'marked within-subject increases in the amplitude and extent of (blood oxygen-level dependent) BOLD activity' on one of the cognitive tasks. The authors suggest: 'in cases of mild concussions, such as those reported here and elsewhere in which little if any decrement in performance is observed, compensation in the neural network recruited during cognitive engagement seems to be required to maintain pre-injury performance levels' [86].

In terms of Satz's BRC model, our recently published work [61] and that of others [64,69,82,83,85] provide further support for the notion that in the presence of mTBI, stress reduces BRC below the FIT threshold, so that otherwise unmeasurable deficits become apparent. NH may be particularly useful as a stress paradigm for mTBI assessment for several reasons. Most of the literature investigating the hypoxia-induced effects on sensory-integrative function has been limited to normally functioning individuals, however, our work [60,61] and that of others [59], demonstrate that, when challenged with hypoxic stress, individuals with mTBI show a statistically significant and disproportionate cognitive impairment as compared with healthy individuals, consistent with the BRC model. Furthermore, Temme *et al.* found that the peripheral oxygenation (SpO_2) response to hypoxia differed between healthy individuals and asymptomatic individuals with a history of mTBI, suggesting that the assessment of additional functional modalities (i.e., oculomotor, pupillometric, vestibular, auditory, etc.) may further enhance the sensitivity and specificity of mTBI assessment [78]. Therefore, while cognitive difficulties attributable to mTBI may be misdiagnosed when examining mTBI individuals using conventional clinical measures, examinations using a stress paradigm may help identify latent symptoms by consuming portions of the BRC, driving capacity below the FIT. Furthermore, the need for increased cerebral resources to maintain normal performance in mTBI, and the inability to do so under hypoxic conditions, would diminish central processing and integration of the sensory inputs and neural projections, including the nuclei at the level of the brainstem, thalamus, frontal lobe, basal ganglia, superior colliculus and the cerebellum, potentially resulting in disproportionate auditory, vestibular, oculomotor, pupillometric and ANS regulation deficits in mTBI individuals, further supporting the use of multimodal assessments.

Comprehensive multimodal mTBI assessment

NH may be useful for examining additional modalities affected by mTBI. In addition to potentially disproportionate deficits in cognitive, oculomotor, pupillometric and ANS functions in mTBI individuals, deficits in vestibular and central auditory processing functions may be evoked by a NH stress. This would add to the scope and power of multimodal mTBI assessment. Vestibular function is maintained through CNS integration of afferent visual, somatosensory and vestibular sensory inputs, and efferent muscle contractions. Impairment, injury and/or damage to one of these systems, including vestibular–visual mismatch, can manifest as instability and reduced postural control [72]. Accordingly, measures of postural stability, such as the Balance Error Scoring System and Sensory Organization Test, have demonstrated sensitivity to mTBI [87–89]. Similarly, the neural projections that compose the auditory pathway, including the nuclei at the level of the brainstem, thalamus and cortex, are sensitive to impairment, injury and/or damage and subsequent deficits in auditory processing [90]. As such, measures of auditory-processing disorders, including the modified Quick Speech-in-Noise test, the Staggered Spondaic Words test and the Masking Level Difference test, have been found to be sensitive to mTBI, blast-exposure and brainstem abnormalities [91,92]. Because the CNS requires a supply of oxygen to function, it is reasonable to assume that central processing and integration of the sensory inputs necessary to maintain balance and postural stability and process auditory information would be impaired by hypoxia. Previous studies have cited evidence of hypoxia-induced postural sway [93,94] and hypoxia-reduced equilibrium, primarily as a result of impairments related to visual function [95], and are consistent with a previous study [96] documenting significantly increased anteroposterior sway in the absence of visual cues during both slow-and rapid-onset hypoxia. Furthermore, previous studies also have found hypoxia-related deficits in auditory sensitivity, steady-state responses of auditory-evoked potentials and central auditory processing [97–99], suggesting that, similar to mTBI, hypoxia-mediated deficits involve compromised auditory processing at the level of the brainstem and CNS.

Practical considerations in NH

Additional factors that support the use of a NH stress paradigm in mTBI symptom assessment include the fact that NH has a long history of safety and reproducibility. The aviation community has used NH for research

and training since the early 20th century and it is still widely used today. NH can be generated using commercial, off-the-shelf, computer-controlled technology that occupies a small footprint and is portable, making assessment procedures widely accessible and reproducible. The levels of NH described in the present paper are well within established civilian and military safety guidelines for aircraft passengers. According to Federal Aviation Administration regulations, civilian aircraft passengers are permitted to have time-unlimited exposure to altitudes up to 15,000 ft. altitude [100]. Regarding military standards of altitude exposure, the current US Army flight regulation, AR 95–1 [101], permits unlimited flight for passengers up to 14,000 ft. altitude.

Potential risks and discomforts specifically associated with commercial and military operational altitudes have been previously summarized by Ernsting and King, who state ‘from 10,000 ft. to 15,000 ft. breathing air... The resting subject exhibits few or no signs and has virtually no symptoms. The ability to perform skilled tasks is impaired, however: an effect of which the subject is frequently unaware...’ [102]. However, in some instances, HH at altitudes above 10,000 ft. has been described to cause: respiratory symptoms, including dyspnea; visual symptoms, including blurred, tunnel and/or dimming vision; somatosensory symptoms, including hot/cold flashes and/or paresthesia; physiological symptoms, including vertigo, headache, nausea and/or fatigue/lassitude; and cognitive and psychological symptoms, including difficulty concentrating and/or feelings of apprehension, stress and/or euphoria. The use of NH, as opposed to HH, eliminates the risks associated with conventional HH in that all the research participants (volunteers and technical personnel) are exposed to terrestrial, often MSL, atmospheric pressure at all times. Thus, during the experiment, if there is an emergency that requires the hypoxic individual return to normoxia, the return can be instantaneous. Lingering symptoms of hypoxia within an mTBI population have not been well defined. However, previous studies from this group found that otherwise healthy mTBI and non-mTBI groups did not exhibit or report discomfort or distress at NH equivalents of 8000, 12,000 and 14,000 ft [61,78]. Therefore, while lingering symptoms of NH in otherwise healthy individuals likely are minimal, brief and readily reversible, it should be noted that these studies [61,78] excluded participants for a wide variety of medical co-morbidities, such as cardiovascular, pulmonary, neurological, psychiatric, and hematological illnesses. As such, a determination cannot be made about the potential adverse symptoms hypoxia may elicit when utilized clinically in individuals with additional co-morbidities. However, given

that hypoxia independently alters multiple physiological functions, it is reasonable to assume that the presence of medical co-morbidities may increase the risk of adverse symptoms following hypoxic stress paradigms.

Conclusions & future perspectives

Patients reporting symptoms of mTBI may be more vulnerable to resource depletion. Such resource depletion is less likely to occur in low-stress environments, where patients may expend greater cerebral effort to temporarily compensate for deficits and achieve normal performance. Given the safety and accessibility of NH paradigms, future utilization of NH has the potential to provide the basis for a practical 'brain stress test' analogous to the standard cardiac stress test. Such a practical NH-based brain stress test would be a particularly important adjunct to current low-stress mTBI assessments. Moreover, the NH paradigm is highly conducive to comprehensive multimodal assessment. As discussed above, it is feasible to integrate cognitive, oculomotor, pupillometric, ANS, auditory and vestibular assessment within a single efficient pro-

cedure. However, there is limited literature regarding multimodal assessment of mTBI and even less regarding stress modalities. Any future clinical application of NH stress paradigms in multimodal mTBI assessment will require extensive preclinical investigation.

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Executive summary

- **Parallel symptomatology of mTBI & hypoxia** Mild traumatic brain injury (mTBI) and hypoxic stress, including that induced by normobaric hypoxia (NH), provoke parallel symptomatology across multiple physiological functions. This includes deficits in cognitive function, particularly working memory, oculomotor functions, particularly saccadic and smooth pursuit eye movements, pupillometric functions, particularly the pupillary light reflex, and autonomic nervous system functions, particularly aspects of cardiovascular and cerebrovascular regulatory responses.
- **Using hypoxia in mTBI assessment** The plausibility that mTBI and hypoxic stress may have combinational, and thereby disproportionate, effects and, accordingly, that NH can be used to uncover latent, hidden or subclinical symptoms of concussion are supported from several direct and indirect observations. Indirectly, asymptomatic mTBI individuals have been shown to exhibit clear, but reversible, deficits in short-term memory and judgment within 10 minutes of hypobaric altitude exposure when compared to healthy controls. Direct examination of combinational NH and mTBI effects found that asymptomatic mTBI individuals exhibited significantly greater, but reversible, impairment in short-term visual memory at NH simulation approximating 12,000 ft. above MSL.

Comprehensive multimodal mTBI assessment

- In addition to potentially disproportionate deficits in cognitive, oculomotor, pupillometric and ANS functions in mTBI individuals, deficits in vestibular and central auditory processing functions may be evoked by a NH stress. Vestibular and auditory functions are known to be compromised following mTBI and, because the CNS requires a supply of oxygen to function, it is reasonable to assume that central processing and integration of the sensory inputs necessary to maintain balance and postural stability and process auditory information would be impaired by hypoxia as well. The addition of additional assessment modalities would only serve to increase the scope and power of multimodal mTBI assessment.

Practical considerations in NH

- Additional factors that support the use of a NH stress paradigm in mTBI symptom assessment include the fact that NH has a long history of safety and reproducibility. The aviation community has used NH for research and training since the early 20th century and it is still widely used today. NH can be generated using commercial, off-the-shelf, computer-controlled technology that occupies a small footprint and is portable, making assessment procedures widely accessible and reproducible. Furthermore, the levels of NH needed to evoke disproportionate deficits in mTBI individuals are well within established civilian and military safety guidelines for aircraft passengers and the use of NH, as opposed to hypobaric hypoxia (HH), eliminates the pressure risks associated with conventional HH.

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