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Review

Optical Neuroimaging in Delirium

Shixie Jiang [1,*], Philip A. Efron [2], Esther S. Oh [3,4,5] and Steven T. DeKosky [6]

[1] Department of Psychiatry, University of Florida College of Medicine, Gainesville, FL 32610, USA
[2] Department of Surgery, University of Florida College of Medicine, Gainesville, FL 32610, USA; philip.efron@surgery.ufl.edu
[3] Division of Geriatric Medicine and Gerontology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA; eoh9@jhmi.edu
[4] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
[5] Division of Neuropathology, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
[6] Department of Neurology, University of Florida College of Medicine, Gainesville, FL 32610, USA; dekosky@ufl.edu
* Correspondence: mjiang1@ufl.edu

Abstract: Delirium persists as the most common neuropsychiatric syndrome among medically ill hospitalized patients, yet its neural mechanisms remain poorly understood. The development of neuroimaging biomarkers has been difficult primarily due to the complexities of imaging patients experiencing delirium. Optical imaging techniques, including near-infrared spectroscopy (NIRS) and diffuse optical tomography (DOT), offer promising avenues for investigating delirium's pathophysiology. These modalities uniquely stand out for delirium exploration due to their blend of spatiotemporal resolution, bedside applicability, cost-effectiveness, and potential for real-time monitoring. In this review, we examine the emergence of optical imaging modalities and their pioneering utility in delirium research. With further investment and research efforts, they will become instrumental in our understanding of delirium's pathophysiology and the development of preventive, predictive, and therapeutic strategies.

Keywords: optical imaging; functional neuroimaging; near-infrared spectroscopy; diffuse optical tomography; delirium; encephalopathy

Citation: Jiang, S.; Efron, P.A.; Oh, E.S.; DeKosky, S.T. Optical Neuroimaging in Delirium. *Photonics* **2023**, *10*, 1334. https://doi.org/10.3390/photonics10121334

Received: 28 October 2023
Revised: 22 November 2023
Accepted: 30 November 2023
Published: 1 December 2023

1. Introduction

Delirium is a neuropsychiatric syndrome characterized by an acute or subacute onset and fluctuating course, with disruptions in attention, arousal, multiple cognitive domains, psychomotor state, emotions, and the sleep–wake cycle [1]. It can be precipitated by any type of medical insult (e.g., infections, sepsis, stroke, organ failure) [2]. The pathophysiology is complex and not fully understood, with hypotheses based on derangements in various neurotransmitters, inflammation, oxidative stress, cerebral autoregulation, and functional network dysconnectivity [3]. It is exceedingly common in the medically ill, especially the elderly, and may be present in up to 50% of hospitalized patients over the age of 65 years, with rates as high as 83% in the intensive care unit [4,5]. It is associated with a higher risk of mortality, institutionalization, and incident dementias [6–8]. The estimated annual healthcare cost associated with delirium in the United States ranges from USD 143 billion to USD 150 billion [9]. Currently, there exists no definitive treatment for delirium, and treatment of underlying medical problem(s) driving the episode of delirium is most important [1]. In order to truly advance our approaches to preventing and treating delirium, improving our ability to study underlying neural mechanisms is critical.

Previous structural neuroimaging studies using computed tomography (CT) and magnetic resonance imaging (MRI) have revealed that delirium is associated with grey

matter volume loss and white matter hyperintensities and tract disruption in various brain regions [10–12]. However, these findings are not generalizable nor considered unique to delirium given their non-specific results, heterogeneous cohorts, and limited sample sizes. Advanced functional imaging studies have reported prominent hypoactivity in several cortical regions and dysconnectivity within the default mode and central executive networks [13,14]. Areas within the frontal and cingulate cortex appear to be most implicated in delirium, with subcortical structures such as the thalamus and caudate involved as well due to their role, along with the ascending reticular activating system, in regulating arousal [15–17]. Notably, these studies have relied on functional MRI (fMRI) and positron emission tomography (PET); however, their sample sizes are even smaller than many structural imaging studies. Moreover, PET requires fasting and an extended uptake period prior to imaging, which is not realistic for many delirious patients. With all MRI, CT, and PET modalities, the major limitations are lack of portability and diminished patient tolerability given their acutely ill status and severity of psychomotor and cognitive impairment. Electroencephalography (EEG) has been widely implemented given its portability; however, its use is limited to detection and basic regional and network analyses due to its low spatial resolution [18]. One proposed solution to the challenge of delirium neuroimaging has arisen with the advent of optical imaging techniques.

Optical Imaging

In 1977, Frans Jöbsis pioneered the feasibility of measuring changes in blood and tissue oxygenation within the brain of a living organism using near-infrared (NIR) light [19]. Since then, optical neuroimaging has evolved into a diverse field of research with numerous basic science, translational, and clinical studies capitalizing on light's unique features for brain imaging. NIR light can provide crucial functional imaging data by detecting intrinsic alterations in absorption, fluorescence, or scattering. Additionally, a wide range of exogenous contrast media can be employed to gather additional information [20]. Commonly measured chromophores include oxy- and deoxyhemoglobin, cytochromes, and metabolites, all capturing indicators of brain functional activation akin to traditional functional imaging methods [21]. Optical imaging presents several advantages over standard functional imaging techniques, such as real-time capabilities, minimized subject movement constraints, a broader selection of contrast agents, absence of ionizing radiation, reduced costs, and enhanced portability [20]. For the study of delirium, two important optical imaging techniques that should be investigated are functional near-infrared spectroscopy (fNIRS) and diffuse optical tomography (DOT).

Functional near-infrared spectroscopy (fNIRS) is grounded in the fundamental principles of NIR spectroscopy, and the descriptor "functional" was ascribed following its inaugural application in early human studies [22,23]. fNIRS can concurrently assess changes in the optical characteristics of the human cortex from multiple measurement sites, with outcomes visualized as a topographical map or image covering a specific region. This technique capitalizes on the transparency of human tissues to NIR light within the spectral range of 650–1000 nm, where chromophores (e.g., hemoglobin in small blood vessels) effectively absorb or scatter NIR light [24]. Through quantifying oxyhemoglobin increments and concurrent deoxyhemoglobin reductions, fNIRS captures immediate indicators of heightened local arteriolar vasodilation, leading to increased local cerebral blood flow and volume in targeted regions. This hemodynamic response reflects neurovascular coupling, serving as a proxy for neuronal activity in the brain [25]. Numerous companies offer multi-channeled fNIRS devices at a fraction of the cost of an fMRI machine. Due to their compact interface and user-friendly setup, these devices are easily operated and switched from one patient to another [26].

Diffuse optical tomography (DOT) represents a contemporary noninvasive NIR-based method akin to the analogy between magnetic resonance spectroscopy and magnetic resonance imaging (MRI). In contrast to the two-dimensional topographical approach of fNIRS, DOT employs multiple near-infrared wavelengths and overlapping channels, accompanied

by diverse source–detector distances for data collection [27]. This enables the quantification of hemodynamic responses at varying brain depths and the creation of high-resolution three-dimensional images [28]. Consequently, DOT offers a compelling alternative for three-dimensional functional neuroimaging, even in comparison to fMRI. While both modalities target blood oxygen-level dependent (BOLD) signals, the distinction lies in fMRI's reliance on predominantly measuring de-oxyhemoglobin [29]. Additionally, DOT's capacity to concurrently capture all hemoglobin signal types facilitates the differentiation of timing, localization, and neurovascular coupling magnitude, enhancing the depiction of dynamic brain changes beyond fMRI capabilities [30–32]. Much like fNIRS, DOT is cost-effective, portable, and mobile, and the advent of wearable DOT systems with increasingly adaptable interfaces is on the horizon [33–37].

2. Optical Imaging in Delirium

To date, NIRS has been used in several delirium studies with a focus on intensive care unit (ICU) populations and sepsis as the primary etiology of delirium. Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [38]. It is exceedingly common in the ICU, with rates as high as 39.3% based on pooled global data [39]. The pathophysiology of sepsis-associated delirium is not well understood; however, impairment in cerebral oxygenation, perfusion, and autoregulation is hypothesized as a major contributor [40]. As such, NIRS has played a pivotal role in preliminary studies investigating this mechanism underlying delirium related to sepsis in the ICU. Table 1 provides a summary of the available studies that have implemented NIRS in the study of delirium.

In 2008, Pfister et al. were the first to demonstrate the potential for the application of optical imaging in the exploration of delirium pathophysiology [41]. A total of 23 patients were enrolled, with 16 included for final analysis and 12 diagnosed with delirium based on the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [5] assessments. A tissue oxygenation index (TOI) was used as a surrogate marker for cerebral oxygenation, captured by bilateral NIRS over the frontal to frontoparietal area for one hour within 48 h of ICU admission. No conclusive differences in TOI were found between delirious and non-delirious patients. Interestingly, blood flow velocity and regulatory changes captured by separate transcranial Doppler ultrasounds did demonstrate significant differences in the two groups. The authors offered several explanations, including sample size, limited optode placement (two channels), and lack of simultaneous Doppler measurements with NIRS.

Three subsequent pilot studies from other groups were able to further elucidate this potential mechanism related to sepsis and delirium. Funk et al. applied a similar protocol with 15 patients enrolled, and 7 were reported to be CAM-ICU positive for delirium [42]. Bilateral frontal NIRS was applied to measure tissue oxygen saturation (cut-off of 65%) for 24–48 h within 12 h of ICU admission. Their study reinforced a lack of relationship between tissue oxygen saturation and incidence of delirium; however, the authors questioned whether their cut-off was truly sensitive for delirium and expressed concerns regarding cerebral edema confounding their results given the status of their patients. Conversely, Wood et al. conducted an initial study using single forehead NIRS in 10 patients (5 screened as delirious) [43]. Non-delirious patients were found to have a higher level of brain tissue oxygenation (BtO_2) compared to delirious patients. Compared to the previous studies, Wood et al. extended the observation time by performing continuous NIRS monitoring for the first 72 h of sepsis onset and suggested that the timing of NIRS measurements (during the initial resuscitative phase) may be important given fluctuations in tissue oxygenation related to delirium. These results were confirmed by Vasko et al. in a study comparing cerebral oxygenation between 15 septic patients and 10 age- and sex-matched controls [44]. Bilateral frontal NIRS demonstrated significantly lower oxygenation saturation levels in septic and delirious patients.

The first large prospective cohort study that focused on using NIRS for monitoring the development of delirium was conducted by Wood et al. in their follow-up trial (The Cerebral Oxygenation and Neurological outcomes Following CriticAL illness (CONFOCAL) study) [45]. A total of 88 adult patients in the ICU were enrolled and monitored with a single forehead NIRS sensor for the first 24 h of their admission. Patients were screened daily for delirium, with 30 days set as the maximum enrollment period. Their analyses reinforced and extended their pilot results, demonstrating a significant negative association between BtO_2 and the proportion of ICU time spent delirious. BtO_2 was also found to be an independent predictor of delirium, irrespective of other confounders. An important secondary outcome reported that BtO_2 levels possessed no relationship with peripheral hemodynamic parameters, suggesting an independent mechanism of cerebral autoregulation. A subsequent study based on CONFOCAL data focused on cerebral autoregulation, specifically by measuring the cerebral oximetry index (COx) [46]. COx was defined as a time-varying correlation coefficient between mean arterial pressure (MAP) and NIRS-derived BtO_2, with positive values reflecting dysfunctional cerebral autoregulation. Single forehead sensor NIRS measurements were obtained from 40 patients, and COx values were computed from the first 72 h of their ICU admission. Their results showed that the duration of cerebral autoregulation dysfunction within this early resuscitative phase of their ICU stay was an independent risk factor for the development of delirium. Optimization of MAP values to preserve the COx was suggested as a future research direction.

Based on the results of CONFOCAL, Rosenblatt et al. published a case series exploring the relationship between the optimization of MAP based on COx values and delirium severity [47]. Six patients with sepsis-induced delirium underwent 12 h of bilateral frontal NIRS monitoring during the first 48 h of their admission. Delirium severity was estimated based on the Glascow Coma Scale [48] scores. Hourly COx measurements were found to be consistently higher in delirious patients with lower GCS scores. Additionally, high individual variability in MAP values was demonstrated, suggesting a necessity to perform continuous monitoring that is personalized for each patient. Thus, the authors asserted that the universal MAP goal of $\geq$65 mm Hg in sepsis [49] may not apply to every individual and should be individually optimized.

In terms of advanced functional neuroimaging studies, there are few studies, including one published fNIRS study and one preliminary DOT study. Yoshimura et al. (2017) conducted a trial with 58 patients with end-stage liver disease (ESLD) and 28 healthy controls [50]. A total of 50 of the 58 patients with ESLD were recruited from a clinic, and 12 were diagnosed with delirium. Delirium severity was measured with the Delirium Rating Scale—Revised 98 (DRS-R98). A 52-channel fNIRS device (wavelengths 695 and 830 nm) measured hemoglobin values in the bilateral prefrontal cortical region. Subjects were instructed to perform a modified version of a Verbal Fluency Task (VFT) during fNIRS measurements. Their results demonstrated significantly reduced oxygenated hemoglobin (oxy-Hb) in delirious patients and patients with ESLD compared to controls; however, those with delirium exhibited the lowest values. No correlation was observed between DRS-R98 scores and oxy-Hb during the VFT. These findings demonstrated a potential optical imaging biomarker for delirium, although no follow-up study has been reported yet.

For DOT, our group has published preliminary results in a small cohort of delirious subjects (n = 5) and age/gender/handedness/admission setting-matched non-delirious subjects (n = 5) [51]. We built a custom 48-channel DOT device with a lighter mesh and lower-density optical fibers in order to enable its use at bedside in hospitalized delirious patients. Patients were recruited from the ICU and general wards of a single tertiary academic hospital. The DOT interface was centered on the bilateral prefrontal cortex, with a focus on the dorsolateral and dorsomedial prefrontal cortex. The Months Backwards Test was conducted during imaging, given its validation as a test of attention, working memory, executive function, and processing speed in delirium and dementias [52]. Subjects were imaged at the time of their initial delirium episode and again after the resolution

of delirium. DRS-R98 scores were also conducted at these two time points. Our results demonstrated significantly lower total and oxygenated hemoglobin values during delirium and even remained low after the resolution of delirium when compared to their matched controls. As such, the three-dimensional and bedside capabilities of DOT may prove to be a critical tool in the validation of optical neuroimaging biomarkers in delirium and to potentially study the longer-term cognitive decline that occurs post-delirium.

Table 1. Summary of published studies using optical neuroimaging in delirium.

Reference	Clinical Setting	Sample Size	Delirium Etiology	Optical Imaging Technique	Imaging Site(s)	Results
Pfister et al., 2008 [41]	ICU	23 (12 delirious)	Sepsis	NIRS	Bilateral frontal to frontoparietal	No difference in TOI between delirious and non-delirious patients; however, blood flow velocity measured by Doppler did differ
Funk et al., 2016 [42]	ICU	15 (7 delirious)	Sepsis	NIRS	Bilateral frontal	No difference in TOI between delirious and non-delirious patients
Wood et al., 2016 [43]	ICU	10 (5 delirious)	Sepsis	NIRS	Single frontal (forehead)	Non-delirious patients demonstrated a higher frequency of BtO_2 compared to delirious patients
Vasko et al., 2014 [44]	ICU and clinic	15 delirious; 10 controls	Sepsis	NIRS	Bilateral frontal	Delirious and septic patients exhibited a lower BtO_2 compared to controls
Wood et al., 2017 [45]	ICU	88 (19 delirious)	Sepsis	NIRS	Single frontal (forehead)	Significant negative association between BtO_2 and proportion of time spent delirious
Lee et al., 2019 [46]	ICU	40 (24 delirious)	Sepsis	NIRS	Single frontal (forehead)	Duration and level of COx correlates with prediction of delirium
Rosenblatt et al., 2020 [47]	ICU	6 delirious	Sepsis	NIRS	Bilateral frontal	COx measurements higher in more severe delirium
Yoshimura et al., 2017 [50]	Clinic	58 with ESLD (12 delirious); 29 controls	ESLD	fNIRS	Bilateral prefrontal cortex	Significantly reduced oxy-Hb values in ESLD, and even more so in those with ESLD and delirium, compared to controls
Jiang et al., 2022 [51]	ICU and general wards	5 delirious; 5 matched controls	Heterogeneous	DOT	Bilateral prefrontal cortex	Significantly reduced oxy-Hb and total Hb during delirium and even post-resolution of delirium compared to controls. Lower total Hb correlated with higher severity of delirium

Abbreviations: ICU = intensive care unit; NIRS = near-infrared spectroscopy; TOI = tissue oxygenation index; BtO_2 = brain tissue oxygenation; COx = cerebral oximetry index; ESLD = end stage liver disease; Hb = hemoglobin; oxy-Hb = oxygenated hemoglobin; NIRS = near-infrared spectroscopy; fNIRS = functional near-infrared spectroscopy; DOT = diffuse optical tomography.

3. Challenges and Limitations

While optical imaging holds substantial promise in the context of delirium, several hurdles must be addressed to propel the advancement of these methodologies.

The complexity and multifaceted nature of the depth sensitivity and penetration limits of NIR light constitute an intricate and difficult topic. These attributes are contingent upon numerous factors inherent in NIRS applications, encompassing the technology, parameters, and neuroanatomical characteristics of the subjects or tissues under examination. These elements all possess significant influence over the physical characteristics of light absorption

and scattering within the brain, with distinct depths exhibiting dynamic coefficient variations necessitating specific computations [25,26]. The feasible imaging depth, particularly with commercial NIRS devices, is typically estimated to be within the 2–3 cm range beneath the scalp surface [53–55]. When higher wavelengths (808 nm or beyond) are employed, reports indicate the potential for imaging at depths of 4–5 cm [56–58]. DOT, with its advanced signal properties and sophisticated software interface, consistently demonstrates the capability to produce images at these greater depths, in contrast to fNIRS [27,59,60]. Furthermore, recent experiments involving time- or frequency-domain detection modes show promise in alleviating some of the depth sensitivity constraints inherent to the conventional continuous-wave design [61]. Nevertheless, this issue undeniably constrains the utility of NIR light for imaging deeper brain structures, which holds some significance for completely understanding delirium. For instance, subcortical structures such as the thalamus and caudate have been proposed to contribute to disturbances of arousal, given their association with the ascending reticular activating system [15,17].

A prevalent challenge shared by all functional neuroimaging methods is their susceptibility to motion artifacts. The subtle nature of changes in blood oxygenation and blood flow linked to neural activity relative to motion-induced signal alterations creates difficulties in interpreting hemodynamic responses within specific regions [62]. Such artifacts can diminish image quality, leading to skewed statistical analyses and erroneous conclusions [63]. During optical neuroimaging procedures, motion that occurs between the optical fiber and the subject's scalp can adversely impact image acquisition, causing decoupling and fluctuations in the recorded optical signal [64]. The most common motion artifact manifests as a brief, high-amplitude intensity change, promptly subsiding after the motion ceases. In the case of fMRI, whole datasets can become unusable, depending on the magnitude of motion during data acquisition when this type of artifact occurs. However, when using NIRS or DOT, temporary, unaffected data segments can still be captured and effectively utilized for analysis, given their higher tolerance for head and scalp motion, primarily due to differences in interface design [65]. This tolerance is likely attributable to algorithm variations and the use of mesh-based headgear with customized optode–scalp distances, as opposed to fMRI's fixed and rigid design. Conventional techniques for mitigating excessive motion artifacts include meticulous optode array design, minimizing subject motion through visual fixation, reducing stimuli, ensuring comfortable positioning, and employing advanced post-processing methods [27]. Newer computational methods for reducing motion artifacts, outside of traditional filters and channel regression, also exist and include temporal derivative distribution repair, transient artifact reduction algorithms, and dual-stage median filters [66]. For applications in delirium, optical imaging holds promise in investigating hyperactive delirium or delirious agitation, given the decreased sensitivity to motion artifacts. All previous studies have predominantly focused on hypoactive delirium as patients with agitation are unlikely to tolerate prolonged neuroimaging scans. The pathophysiology and underlying neural mechanisms may differ immensely between types of delirium, and these disruptions remain a worthy area of investigation for NIRS and DOT.

4. Future Directions

The majority of available studies have focused on NIRS and not fNIRS or DOT. This distinction is important as NIRS typically involves a limited number of channels; thus, it is only able to acquire data from a portion of the region of interest. Only one- or two-channel NIRS placed over the forehead was used in all of the reported sepsis-induced delirium studies. As such, the cerebral oxygenation and functional activity captured only represented a very limited area of the frontal cortex. With the denser optode arrays of fNIRS and DOT, larger regions of the brain can be assessed simultaneously, and connectivity analyses can be conducted, similar to fMRI approaches [67,68]. Network analyses are critical for advancing our research in delirium, as it is unlikely that only the frontal lobe is dysregulated. Based on previous EEG, fMRI, and PET studies, the parietal and temporal lobes can be involved

as well [16–18]. For instance, given the prominent disruption of attention in all types of delirium, mapping functional dysconnectivity for this symptom alone involves multiple areas: the medical prefrontal cortex, lateral prefrontal cortex, anterior inferior parietal lobule, and precuneus [69]. Utilizing such an approach would open a frontier for further subtyping of delirium, predictive modeling based on abnormal networks, and targeted clinical interventions potentially based on personalized mapping. Whole cortex fNIRS and DOT interfaces have recently been created that would be ideal for studying all of these regions and network connectivity in delirium. These devices involve over 100 channels and have been reported to still be lightweight and portable for human studies [33,70,71].

In terms of clinical analyses, neuroimaging studies in delirium have also been limited as they almost exclusively focus on hypoactive delirium. These patients exhibit significant psychomotor slowing and, thus, are chosen most likely due to ease of imaging. Hyperactive ("agitated") delirium involves serious agitation and inability to tolerate even routine medical care, let alone imaging in an MRI or CT machine [1]. The pathophysiology and brain regions involved may very well be different between delirium subtypes; however, this has remained unexplored in imaging biomarker studies due to a lack of patient tolerability in hyperactive delirium.

Optical imaging is advantageous for investigating hyperactive delirium further for several reasons. The bedside capabilities of these devices allow for naturalistic studies and bypass logistical requirements regarding transportation for imaging and tolerability concerns. However, it should be noted that in severe cases, standard optical imaging devices utilizing fiber optics would still suffer from significant motion artifacts. Modern techniques have developed fiberless technology, which refers to interfaces built with cabled systems, flex-rigid printed circuit boards, and modular systems. The number of channels is more limited than fiber-based arrays, but several devices have been created with zero tethering and validated for advanced functional data acquisition [70]. Such truly wireless devices would be ideal for not only studying hyperactive delirium but also for examining how certain interventions, such as physical and occupation therapy exercises, may improve delirium outcomes as researchers would be able to conduct functional analyses during activity. This would potentially allow for further refinement and personalization of delirium treatments.

In addition to the study of delirium in adults, the application of optical imaging in the pediatric population may hold promise as well. Delirium develops in approximately 25% of children admitted to the pediatric ICU [72]. The neuropsychiatric symptoms that occur in older children can appear similar to those observed in adults; however, the symptoms and diagnosis of delirium in neonates are more difficult. Validated screening tools are not as accurate compared to their adult counterparts [73]. The use of fNIRS or DOT is an attractive option for the study of delirium in neonates, in particular, given their smaller skull and brain morphology, thus allowing for ease of administration and whole brain imaging interfaces at lower expenses. Only two published pilot studies have evaluated the use of NIRS in children with emergence delirium (related to anesthesia), but not in ICU delirium or other common hospital-derived subtypes. Their preliminary results reinforce the conceptual innovation of optical imaging in this specific delirium population, given oxygenation deficit differences between children with and without delirium [74,75].

Finally, the development of other types of optical imaging biomarkers may play an essential role in delirium pathophysiology. The overwhelming majority of optical neuroimaging investigations concerning delirium have relied on absorption-based methodologies to gauge hemoglobin as the primary focal chromophore. However, there exist other chromophores with potential applicability in assessing functional brain activity. Cytochrome c oxidase (COx) is a noteworthy example, serving as the ultimate enzyme in the mitochondria's electron transport chain. It is responsible for preserving the transmembrane proton gradient crucial for adenosine triphosphate (ATP) synthesis, the chief source of cellular energy [76]. Interestingly, mitochondrial dysfunction has been associated with sepsis-induced organ failure in previous studies [77]. Moreover, mitochondria have been

implicated in the pathogenesis of Alzheimer's disease and other forms of neurodegeneration [78,79]. Based on this evidence, a 2019 study by Samuels et al. demonstrated that variations in mitochondrial DNA were associated with development and protection from delirium in certain ethnic groups [80]. Their results propose an entirely novel avenue for the application of fNIRS and DOT for correlating COx activity with delirium propagation, especially given the role of mitochondria in regulating oxygenation.

5. Conclusions

Substantial efforts are required to ameliorate the adverse outcomes associated with delirium. Optical neuroimaging techniques are highly promising tools for the study of delirium and the development of approaches for expanding our knowledge of pathophysiology and clinical approaches to delirium. What sets them apart in this context is their unique combination of high resolution, portability, real-time capabilities, and cost-effectiveness. Currently, no other method offers all these attributes simultaneously, particularly when it comes to imaging delirious patients. An increasing body of initial research reports emphasizes the successful application of NIRS, fNIRS, and DOT in delirium. With further investment and research efforts, the significance of these methods is poised to become pivotal for enhancing our understanding of delirium's pathophysiology and the development of preventive, predictive, and therapeutic strategies.

Author Contributions: S.J. conceived and drafted the manuscript; P.A.E., E.S.O. and S.T.D. provided supervision and contributed revisions to the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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