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Ultraweak Photon Emission in the Nervous System: Mechanisms, Disease Relevance, and Translational Opportunities

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Abstract

Ultraweak photon emission (UPE) refers to spontaneous, low-intensity photon release from biological systems, generated largely through oxidative metabolic reactions involving reactive oxygen species, lipid peroxidation, mitochondrial activity, and electronically excited molecular intermediates. Because the nervous system is highly metabolically active and vulnerable to oxidative stress, hypoxia, excitotoxicity, inflammation, and mitochondrial dysfunction, UPE may offer a noninvasive optical window into neural physiology and disease. In this narrative review, we examine experimental and translational evidence linking UPE to nervous system function, with emphasis on neuronal excitation, glutamate-mediated activity, ischemia-reperfusion injury, stroke, neurodegeneration, mental-state and anesthesia paradigms, photobiomodulation, demyelinating disease, Parkinson disease, amyotrophic lateral sclerosis, and neuro-oncology. Across these domains, UPE appears most consistently associated with redox metabolism, mitochondrial function, oxidative stress, and excitation–metabolism coupling, whereas evidence that endogenous photons mediate functional neural signaling remains preliminary. Current data suggest that UPE may be most promising as a preclinical biomarker of tissue metabolic state, delayed post-ischemic dysfunction, and early neurodegenerative change, particularly when integrated with electrophysiology, perfusion imaging, molecular assays, and other physiologic measures. However, clinical translation is limited by low photon flux, limited temporal and spectral resolution, difficulty localizing signals from deep tissue, heterogeneous experimental protocols, and incomplete source attribution. Overall, UPE represents a promising but still early-stage framework for studying nervous system metabolism and disease, with future progress dependent on standardized methods, multimodal validation, and disease-specific investigation.

Keywords: ultraweak photon emission; neural biophotons; central nervous system; oxidative metabolism; reactive oxygen species

1. Introduction

Ultraweak photon emission (UPE)—spontaneous, non-thermal photon emission from living systems—is often traced conceptually to Alexander Gurwitsch's 1920s 'mitogenetic radiation' experiments, where onion root tips reportedly altered mitotic activity in nearby roots when separated by quartz (but not an opaque barrier), suggesting an extremely weak radiative signal, possibly in the ultraviolet (UV) range[1]. His research alluded to optical communication pathways within biological systems on the cellular level. This seminal experiment sparked nearly a century of controversy[2]. Later studies using more sensitive photomultiplier tubes (PMTs) and charge-coupled devices (CCDs) confirmed that all biological tissues emit measurable photons in the visible to near-infrared range at intensities around 10-16–10-18 W/cm², spawning subsequent studies investigating the role of UPE as a biomarker of health and disease[3]. The role of UPE in cellular communication, as Gurwitch's

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research implied, has remained controversial. A number of studies have shown potential UPE-based communication both within and between cells under chemically isolated but optically coupled conditions, including neutrophil respiratory burst activation by other neutrophils, mouse fibroblasts, human microvascular endothelial cells; and human colorectal epithelial cells modulating one another's growth; and antimycin-stressed mitochondria affecting the oxygen consumption of other mitochondria, among other examples[4–6].

UPE have been detected from wavelengths ranging from UV to infrared, and are generally understood to arise as excited molecular intermediates relax from high to low energy states[7]. The dominant mechanism is thought to involve reactive oxygen species (ROS) including superoxide, hydrogen peroxide, hydroxyl radicals, and singlet oxygen, which are produced during mitochondrial respiration among other pathways[8]. Subsequent reactions between ROS and other biomolecules like lipids and proteins generate excited carbonyls and other species, which are then also thought to emit UPE. Mitochondria are thus considered the chief source in eukaryotes, through electron transport chain leakage (superoxide: 634, 703, 1270 nm), and lipid peroxidation (excited carbonyls: 350-550 nm)[8–11]. Furthermore, UPE also has been shown to increase with oxidative stress as ROS levels increase[8]. Other contributors have been proposed including catecholamine and aromatic amino acid oxidation, melanin synthesis, and peroxisome reactions[12,13]. UPE has been measured in vitro and in vivo from a variety of tissues and organisms using photon counting devices, such as PMTs, charge-coupled devices (CCDs), and more recently electron multiplying CCD (EMCCD) cameras[14–16]. Histological detection of UPE using silver nitrite nanoparticles has also been described in neural tissue specifically[17].

The known sources of UPE—closely linked to oxidative metabolism, inflammation, mitochondrial dysfunction, and reactive oxygen species—suggest potential relevance to medicine. These processes contribute to the pathogenesis of many disorders, including diseases of the nervous system, where metabolic dysregulation, hypoxia, and excitotoxicity are prominent. Accordingly, UPE has been proposed as a candidate diagnostic biomarker. Moreover, if UPE-mediated cellular signaling is validated, defining these mechanisms could open therapeutic avenues that mimic or modulate endogenous optical signals and their downstream pathways. Yet, despite substantial experimental interest, clinical translation of UPE remains limited. This review therefore examines the evidence linking UPE to neurologic disease and identifies the most promising directions for research aimed at clinically actionable use cases. We focus on disorders of the nervous system and neuroscience applications with plausible translational relevance, given the concentration of UPE work in this domain and the urgent need for improved diagnostics and therapeutics. Where relevant, we also consider exogenous light-based interventions—most commonly photobiomodulation (PBM)—to evaluate potential mechanistic overlap and to situate UPE within a broader optical model of physiology and disease.

2. Mechanisms and Experimental Basis of Neural UPE

2.1. UPE and the Brain

A substantial portion of UPE research has focused on the nervous system, yielding findings that appear less well described in other tissues. The first direct evidence of neural UPE came from hippocampal slice experiments: potassium-induced depolarization increased UPE, whereas sodium-channel blockade with tetrodotoxin (TTX) suppressed it, indicating that neuronal activity can modulate the UPE emission profile. Neuronal UPE has also been linked to oxidative metabolism, consistent with observations in other cell types[10]. In the same work, rotenone (a complex I inhibitor) initially reduced emission but was followed by a delayed rebound, implicating electron leakage from the electron transport chain—with downstream singlet oxygen formation—as a plausible dominant photon source. Finally, UPE has been reported to correlate with EEG activity, particularly very slow (<1 Hz) rhythms, potentially reflecting delayed metabolic dynamics[18].

Like other cell types, measured neuronal UPE extends primarily from 350-700 nm and occasionally to 1300 nm[9,12,14,16]. In mouse models of both aging and neurodegeneration,

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glutamate induced UPE exhibits a significant blueshift[19,20]. Across species, human neural tissue was shown in one study to be redshifted compared to other species, with humans, monkeys, and pigs showing a redshift compared to bullfrogs, mice, and chickens[21].

In addition to the cellular mechanisms implicated in the generation mentioned above, such as mitochondrial ROS, the nervous system has demonstrated several unique UPE emission patterns. Notably, axons and nodes of Ranvier appear to emit light during electrical stimulation, measured using silver-autography, suggesting activity-dependent emission along white matter tracts[17].

Beyond emission alone, however, several theoretical and computational studies have proposed that myelinated axons could act as optical waveguides, channeling photons in the visible to near-infrared range with minimal loss, depending on myelin geometry and refractive indices[22–25]. Direct experimental evidence of this hypothesis is limited, but at minimum it demonstrates that neural tissue possesses optical properties which alter photon propagation, either incidentally or as a method of transmission. Proponents of this hypothesis also point to the presence of photosensitive molecules in neurons such as the fluorescent neurotransmitters (serotonin, norepinephrine, and dopamine), chromophores such as flavins and aromatic amino acids, as well as relative speed of light propagation, and ability of photons to transmit information in the form of wavelength, frequency, and intensity, which may offer efficient information transfer. Interestingly, it has also been pointed out that microtubules contain vast networks of photosensitive tryptophan rings, which may channel or absorb UPE.

Whether photons contribute to functional signaling in the nervous system or are simply markers of underlying redox metabolism remains unclear. In either case, their measurement might provide valuable information about the physiologic and pathophysiologic state of the nervous system, making them a promising biomarker candidate. This idea will be explored in subsequent sections, specifically in relation to disorders of the nervous system.

2.2. Neuronal Excitation and Excitotoxicity

Having established that neural tissue emits UPE in accordance with metabolic and electrical activity, it is now critical to understand how UPE changes with various external conditions and stressors. Excitotoxicity, or the overactivation of glutamate, especially in AMPA and NMDA receptors, is ubiquitous in a number of nervous system pathologies, including stroke, epilepsy, neurodegeneration, multiple sclerosis, and schizophrenia, and mood disorders[26–29]. Therefore, understanding how UPE as a potential new biomarker relates to neuronal excitation is critical in evaluating its utility. Activity-dependent UPE in the mammalian brain was first shown in rat hippocampal slices. Depolarization with high concentrations of potassium increased photon emission while TTX reduced it, and signal magnitude tracked tissue oxygen consumption, indicating a mitochondrial source[30]. This established UPE as a biomarker of neuronal metabolism, setting the stage for later perturbation and synaptic and circuit propagation studies.

One such study demonstrated the intimate relationship between UPE and neuronal excitation through a series of metabolic perturbations in cultured rat cerebellar granule neurons as measured with a photomultiplier tube[16]. Adding a high extracellular concentration of potassium, causing depolarization, led to a marked increase in UPE (roughly a >20% rise in emission within the 310–520 nm range), suggesting UPE is dependent on neuronal activity. Furthermore, TTX application, by blocking the sodium channels needed for neuronal activation, suppressed potassium induced UPE emission (by approximately 18%). Removing extracellular calcium from solution had a similar effect (reducing UPE by about 30%), potentially by preventing neurotransmitter release. 2,4-dinitrophenylhydrazine (DNPH), which quenches oxidized molecules, almost completely abolished UPE (a nearly 100% suppression), confirming that oxidized molecules were their source. At the same time, slice models of ischemia-refusion have shown that prolonged K^+ depolarization can cause an initial rise in UPE followed by depression below baseline, which suggests that the net response to K^+ may depend on whether energetic demand or metabolic failure predominate[10].

Tang and Dai expanded on this line of inquiry, bathing coronal brain slices in a solution containing glutamate which gradually increased UPE, peaking around 90 minutes and persisting for

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200 minutes[15]. These researchers showed that glutamate-evoked UPE follows a reproducible temporal pattern characterized by an initiation phase and a sustained maintenance phase. The increase in UPE was almost completely attenuated by glucose or oxygen deprivation, as well as by sodium azide, a cytochrome c oxidase inhibitor, demonstrating the importance of mitochondrial oxidative metabolism in this process. In contrast, action potential blockade with TTX, anesthetic exposure with procaine, and removal of intra- or extracellular calcium only partially reduced glutamate-induced biophotonic activity. These findings suggest that while neuronal electrical activity and calcium signaling contribute to UPE generation, a substantial component may arise from metabolic processes that persist independently of action potential firing. Notably, the initiation phase persisted even when action potential generation and calcium influx were blocked, whereas sustained maintenance of elevated UPE appeared more dependent on action potentials, calcium signaling, and intact oxidative metabolism. A second glutamate application evoked a faster and larger response, suggesting a potential form of photon-mediated metabolic plasticity. In sagittal slices, UPE activity in the corpus callosum and thalamus appeared to originate primarily from axons of cortical neurons, supporting the possibility of UPE propagation along white matter tracts. Similarly, when glutamate was applied to the hippocampal dentate gyrus, UPE increased along its projection areas, lending further support to the idea that biophotonic signals may propagate through defined neural pathways. Interestingly, tau hyperphosphorylation induced by PP2A inhibition decreased UPE activity in axonal regions, suggesting that cytoskeletal integrity may be necessary for efficient UPE transmission. This concept will be further explored in the neurodegeneration section of this paper.

Extending these findings in vivo, methamphetamine (single intraperitoneal dose of 20 mg/kg) administration in rats produced region-specific increases in both ROS and UPE, which were most pronounced in the motor cortex, but also present in the prefrontal, motor, and visual cortices[31]. UPE output closely tracked with malondialdehyde levels, a marker of oxidative stress and lipid peroxidation, which supports a shared source. Mechanistically, methamphetamine is known to stimulate neuronal activity, disrupt mitochondrial function, and increase glutamate and intracellular calcium, all of which drive ROS production. These results demonstrate a direct link between pharmacologic hyperexcitation, oxidative stress, and photon emission.

Several studies have examined how UPE relates to electrical activity at the systems level, namely using EEG. In anesthetized rats, simultaneous EEG and cortical UPE readings demonstrated that emission correlated with θ-band EEG and cerebral oxygenation[14]. In humans, scalp-mounted PMTs and simultaneous EEG showed that extracranially-measured UPE exhibits a <1Hz structure and task specific shifts during eyes-open/eyes-closed tasks, and auditory stimuli. Alpha power correlated weakly and inconsistently with UPE counts, but slow (<1Hz) signature was robust, which suggests that scalp UPE may reflect slow metabolic changes rather than rapid neural firing changes[18]. Another human study reported correlations between UPE and EEG power which tracked with mental imagery several seconds after task onset[32]. This study was limited by a small sample size and warrants further investigation.

Representative mechanistic studies of neural UPE are summarized in Table 1.

Table 1. Main / Foundational Mechanistic Papers of Neural Ultraweak Photon Emission.

Title	Study	Experimental Model / Detection Method	Key Finding(s)	Proposed Mechanism	Relevance to CNS/UPE
Ultraweak biochemilumine scence detected from rat hippocampal slices	Isojima et al., 1995	In vitro rat hippocampal slices; silicon avalanche photodiode (single photon detector)	Early evidence that mammalian neural tissue emits measurable UPE; K^+ increased UPE and TTX suppressed it.	Activity-dependent oxidative metabolism and mitochondrial ROS generate UPE.	Foundational evidence linking neuronal activity to photon emission.

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Activity-dependent neural tissue oxidation emits intrinsic ultraweak photons	Kataoka et al., 2001	Cultured rat cerebellar neurons; Photomultiplier tube (PMT)	Depolarization increased UPE; TTX/Ca^{2+} removal reduced it; DNPH nearly abolished emission.	Oxidized molecules generate UPE in neural cells.	Mechanistic evidence connecting excitation, oxidation, and photon emission.
In vivo imaging of spontaneous ultraweak photon emission from a rat's brain correlated with cerebral energy metabolism and oxidative stress	Kobayashi et al., 1999	In vivo anesthetized rats + brain slices; PMT, EEG	Brain UPE correlated with EEG activity and oxygenation, K^+ increased UPE and decreased glucose suppressed it. Rotenone initially decreased (suspected metabolic block) but then increased UPE (suspected ROS buildup).	Cortical UPE appears to reflect mitochondrial respiration and oxidative stress.	In vivo CNS UPE study supporting metabolic biomarker framework.
Spatiotemporal imaging of glutamate-induced biophotonic activities and transmission in neural circuits	Tang & Dai, 2014b	Mouse brain slices; Electron-measuring Charge Coupled Device (EM-CCD)	Glutamate induced structured biophotonic activity characterized by initiation, maintenance, washout, and reapplication phases. Signals propagated along white matter tracts and hippocampal circuits and were attenuated by microtubule-related perturbation.	Maintenance phase depended on neuronal firing, Ca^{2+} signaling, and oxidative metabolism, while initiation persisted despite blockade, suggesting coupling between metabolic and possible non-canonical photonic processes. PP2A inhibition reduced axonal UPE, implicating cytoskeletal involvement.	Experimental evidence for activity-dependent, circuit-level UPE dynamics; foundation for hypotheses involving axonal and microtubule-associated photonic signaling.
Exploring ultraweak photon emissions as optical markers of brain activity	Casey et al., 2025	Human scalp PMT and EEG recordings	Human scalp UPE showed task-dependent slow oscillatory structure and partial EEG correlations.	UPE likely reflects slow metabolic/redox dynamics rather than direct firing.	Human feasibility study combining EEG and UPE with evidence suggesting metabolic coupling.
Effect of methamphetamine on ultraweak photon emission and level of reactive oxygen species in male rat brain	Esmaeilpour et al., 2023	In vivo rat study; PMT	Methamphetamine increased ROS and UPE in a region-specific manner, strongest in the motor cortex.	Oxidative stress and mitochondrial dysfunction drive photon emission.	Supports UPE as marker of neurotoxic oxidative stress.
Changes in ultraweak photon emission and heart rate variability of epinephrine-injected rats	Yoon et al., 2005	In vivo rat study; PMT, EEG/ECG	Epinephrine altered UPE in parallel with changes in autonomic tone and heart rate variability	Catecholamine oxidation and ROS generation may alter UPE.	Potentially links systemic neurochemical state to photon emission.

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Spectral blueshift of biophotonic activity and transmission in the ageing mouse brain	Chen et al., 2020	Mouse brain slices; biophoton spectral analysis device (BSAD)	Aged mice showed spectral blueshift of glutamate-induced UPE.	Altered NMDA receptor signaling and mitochondrial inefficiency.	Supports spectral UPE changes as markers of altered neural metabolism.
Human high intelligence is involved in spectral redshift of biophotonic activities in the brain	Wang et al., 2016	Human and animal neural tissue	Human neural tissue showed relative redshift of glutamate-induced UPE compared to other animals.	Species-dependent metabolic and signaling differences may alter spectra.	Suggests possible biologically meaningful spectral variation.
Photons detected in the active nerve by photographic technique	Zangari et al., 2021	Excised nerve tissue with silver autography	Electrical stimulation increased photon-related silver deposition at nodes of Ranvier.	Nodal ionic activity and associated processes may generate localized photon emission during axonal conduction.	Supports axonal activity-dependent UPE.
Are there optical communication channels in the brain?	Zarkeshian et al., 2018	Modeling and review	Myelinated axons are speculated to physically support optical waveguiding.	Refractive index properties of myelin could support photon propagation.	Influential waveguide hypothesis paper.
Electromagnetic modeling and simulation of the biophoton propagation in myelinated axon waveguide	Zeng et al., 2022	Simulation/modeling study	Myelin geometry influences optimal photon propagation wavelengths; increased myelination was associated with superior modeled propagation of redshifted light.	Myelinated axons may function as optical waveguides.	May support physical plausibility of neural photonic propagation.
Oxidative species-induced excitonic transport in tubulin aromatic networks: Potential implications for neurodegenerative disease	Kurian et al., 2017	Computational/theoretical modeling	Proposed excitonic energy transfer along microtubule aromatic networks.	Aromatic amino acids within microtubules may absorb oxidative photon energy and support resonance energy transfer, potentially altered by tau-mediated microtubule disruption.	Mechanistic bridge between oxidative stress and microtubule photonics with potential applications to tauopathies.
Biophoton signal transmission and processing in the brain	Tang & Dai 2014a	Narrative review	Summarized evidence for neuronal/glial UPE and potential information processing roles.	Optical waveguiding, chromophore interactions, and photonic coding hypotheses.	Major conceptual framework paper.

3. UPE in Neurologic Disease and Brain States

3.1. Vascular: Ischemia, Reperfusion, and Stroke

Stroke remains one of the most common and devastating neurological injuries[33]. Cerebral ischemia triggers neuronal injury and death through a complex cascade involving energy failure,

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excitotoxicity, inflammation, mitochondrial dysfunction, and oxidative stress. Because UPE originates from electronically excited molecules often generated during redox reactions, ischemia-induced oxidative stress would be expected to produce marked alterations in photon emission. Indeed, cerebral ischemia has been associated with some of the most striking changes in UPE observed in the nervous system, suggesting that UPE may provide a sensitive readout of ischemia-related metabolic and oxidative injury.

In tissue more generally, UPE has been shown to change with ischemia[10,14,34,35]. In human limb models, arterial occlusion reliably produces a significant decrease in UPE, while venous occlusion produces smaller, often nonsignificant reductions. These changes correlate nonlinearly with oxy- and deoxy-hemoglobin measured by near-infrared spectroscopy, suggesting a complex relationship between UPE and oxygenation. It has been pointed out that as hypoxia has been shown to increase ROS, it is unexpected that UPE would decrease. However, current studies utilize limited (e.g., 10 minute) periods of ischemia, and it has been hypothesized that UPE may increase on longer timescales. After perfusion is restored, UPE tends to increase again, though not always fully back to baseline[34,35].

In the brain specifically, Kobayashi and colleagues first demonstrated in vivo cortical imaging of UPE using a two-dimensional photon counting system[10]. This approach detected extremely weak spontaneous cortical emission on the order of ~10^{-16} W/cm² and showed that photon emission decreased by approximately 40% following cardiac arrest, supporting a relationship between UPE, cerebral energy metabolism, and oxidative state. However, the method required prolonged integration times, anesthesia, and an open-skull preparation with parietal bone removal, limiting temporal resolution and reducing its physiologic generalizability to intact-brain conditions.

Building on this platform, as mentioned previously, the same group imaged cortical UPE through the skull of anesthetized rats and showed that intensity correlated with EEG θ-band power and oxygenation status[10]. A shielding experiment confirmed the cortical origin of the signal. A four-vessel forebrain occlusion model dropped UPE significantly (average 138 to 28 counts·mm^{-2}·h^{-1} in the same animal), consistent with decreased oxidative metabolism. Hyperoxia (changing inhaled O2 concentration from 45% to 100%) boosted UPE to ~130% of baseline, decaying gradually upon return to baseline oxygenation, suggesting an increased ROS load that outlasts its stimulus. In rat brain slices, media that raise energy demand or ROS increased UPE (50 mM K^+: transient rise then depression; 10 mM glutamate: sustained rise to ~124% after washout; rotenone/antimycin: delayed, progressive increases), and metabolic deprivation suppressed it (~79% UPE after glucose removal). Together, these studies provided early two-dimensional evidence linking cortical UPE to brain metabolism, EEG activity, and ischemia–reperfusion physiology. However, they were limited by slow imaging speed, which constrained detection of rapid dynamic changes, and by the use of anesthesia, which can alter cerebral blood flow, mitochondrial function, neuronal activity, and oxidative metabolism.

Extending beyond spontaneous UPE, Chai and colleagues used an EMCCD-based system to measure glutamate-evoked UPE in rat brain slices after middle cerebral artery occlusion and reperfusion[36]. Ischemic injury was confirmed in vivo using motor function scores and 2,3,5-triphenyltetrazolium chloride (TTC) staining. Brain slices were then exposed to a sequence of glutamate-stimulation epochs adapted from Tang et al.[15], including sustained glutamate exposure, washout, and glutamate re-application. The sustained exposure phase was used to assess UPE responses associated with oxidative and metabolic load, whereas the washout phase captured residual photon emission after glutamate removal, a signal previously linked to presynaptic vesicle release and neurotransmitter clearance. Finally, the re-application phase served as a second glutamate challenge to probe circuit responsiveness and recovery after the initial stimulation.

At 6 hours after ischemia–reperfusion, Chai et al. observed significant motor deficits and large TTC-defined infarcts, yet glutamate-evoked UPE remained comparable between the ischemic and contralateral hemispheres. By 24 hours, however, UPE was significantly reduced on the ischemia–reperfusion side across stimulation epochs, despite partial improvement in behavioral scores and TTC staining. At 1 week, behavioral performance and TTC staining had largely normalized, but UPE

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was significantly depressed in both hemispheres, with region-specific vulnerability involving the sensory cortex and striatum more prominently than the motor cortex. Notably, these deficits persisted during the wash phase, suggesting delayed presynaptic or circuit-level dysfunction that was not captured by TTC staining or gross behavioral recovery. Consistent with this interpretation, glutamate-evoked UPE has also been reported to be reduced and spectrally blue-shifted in hippocampal synaptosomes from vascular dementia (VaD) models[20], suggesting that chronic small-vessel disease and subacute ischemic injury may share convergent UPE alterations related to impaired synaptic or circuit function.

The UPE dynamics observed during ischemia and reperfusion generally parallel the underlying biochemistry. When oxygen delivery is interrupted, electron transport chain activity is impaired, reducing oxidative metabolic flux and suppressing the formation of photon-generating excited-state intermediates, consistent with the decreased UPE observed during limb and cerebral occlusion. With reperfusion, restored oxygen availability, and particularly hyperoxia, can increase ROS generation and lipid peroxidation, thereby enhancing UPE. In neural tissue, this metabolic signal appears to be layered with an activity-dependent component, whereby membrane depolarization and synaptic drive modulate photon emission and track cortical EEG activity. After stroke, glutamate-evoked UPE becomes persistently depressed, suggesting delayed synaptic or circuit-level dysfunction that may not be captured by gross histologic or behavioral recovery. Together, these findings suggest that post-ischemic brain UPE may serve both as a metabolic reporter of mitochondrial redox state, ROS generation, and lipid peroxidation, and as a functional reporter of synaptic integrity in injured neural circuits.

Photobiomodulation (PBM) with red and near-infrared light has been shown to mitigate ischemic damage in animal models but has had inconclusive evidence in humans thus far. The probable mechanisms of PBM in ischemia model have been described[37–39]. Briefly, PBM is thought to act through photon absorption by intracellular chromophores, principally cytochrome-c oxidase (CCO). This interaction can promote nitric oxide photodissociation, enhance electron transport chain activity, increase ATP production, and modulate ROS generation rather than simply suppressing it. PBM may also support mitochondrial quality control by shifting the balance toward fusion through upregulation of Opa1 and Mfn1 and away from fission through downregulation of Drp1–Fis1/Mff signaling. Importantly, PBM appears to elicit a biphasic redox response, in which an initial transient ROS signal activates downstream antioxidant, cytoprotective, and pro-survival pathways. Beyond mitochondrial effects, PBM may enhance neuronal repair by increasing BDNF expression, thereby supporting neurogenesis, synaptic remodeling, and functional recovery. Red and near-infrared light have also been shown to alter UPE in neural cells in vitro; for example, 660/850 nm light modulated UPE intensity in stressed astrocytes and Neuro-2a cells, reinforcing a potential mechanistic overlap between PBM biology and UPE dynamics[40].

In short, the ischemia–reperfusion literature frames UPE as a potential optical readout of stroke biology: suppression during ischemia, augmentation with reperfusion or hyperoxia, and delayed depression of evoked UPE in post-infarct tissue. PBM engages several neuroprotective mechanisms that overlap with proposed mechanisms of UPE generation, particularly mitochondrial electron transport, redox signaling, and ROS modulation. This overlap suggests that light may be relevant both to the endogenous optical biology of ischemic injury and to the exogenous therapeutic modulation of its downstream complications. However, UPE research in stroke remains limited, and the efficacy of PBM for human stroke has yet to be confirmed. Further work in both areas may support improved diagnostic approaches, such as detecting early metabolic changes through UPE, as well as targeted therapeutic strategies that use persistent post-infarct UPE abnormalities to identify regions of mitochondrial or circuit dysfunction that may benefit from PBM.

3.2. Neurodegeneration

Neurodegenerative disorders pose one of the most devastating global health challenges to date with the burden of these conditions set to rapidly rise with the growing and aging population[41,42]. Alzheimer's disease (AD) alone is estimated to affect 6.9 million Americans over the age of 65 today

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with numbers expected to grow to 13.8 million by 2060[43]. Ongoing research into UPE offers a novel, though still largely preclinical, framework for studying neural activity, synaptic dysfunction, and neurodegenerative disease – which could ultimately drive advancements in diagnostic and therapeutic efforts. Early work by Tang and Dai showed that prolonged glutamate application to mouse brain slices produced sustained increases in biophotonic activity, with signal changes observed along axonal pathways and within hippocampal circuits, suggesting that glutamate-induced UPE may reflect aspects of neural signaling or circuit-level activity. synaptic dysfunction, and neurodegenerative disease[44]. More recently, Wang et al. examined glutamate-induced biophotonic activity in AD and vascular dementia (VaD) models using isolated hippocampal synaptosomes and brain slices[20]. They found that AD and VaD models demonstrated significantly reduced glutamate-induced biophotonic activity and a spectral blueshift compared with wild-type controls; importantly, these changes were partially reversed by pre-perfusion with ifenprodil, a selective antagonist of GluN2B-containing NMDA receptors. These findings suggest that altered UPE may serve as a biophysical correlate of glutamatergic synaptic dysfunction in AD and VaD, and they implicate excessive or dysregulated GluN2B-mediated NMDAR activity as one potential contributor to impaired synaptic signaling. In a related aging study, Chen et al. similarly reported a spectral blueshift in glutamate-induced biophotonic emissions in older mouse brains, which the authors proposed may reflect age-associated changes in neural information processing efficiency[19]. Together, these studies suggest a relationship among glutamatergic signaling, NMDAR/GluN2B function, aging, and disease-associated alterations in UPE. However, because these findings are derived primarily from animal models, isolated synaptosomes, and ex vivo brain slices, further work is needed to determine whether UPE changes are mechanistically involved in cognitive decline or instead reflect broader metabolic and synaptic dysfunction in aging and neurodegenerative disease.

While diminished UPE activity may capture impaired NMDAR-dependent signaling, this represents only one component of the broader molecular network contributing to neurodegenerative disease pathology. In AD, amyloid beta aggregation and tau hyperphosphorylated are accompanied by glial activation, synaptic dysfunction, mitochondrial impairment, oxidative stress, disrupted protein homeostasis, and eventual cell apoptosis and neuronal loss[45]. Because UPE can arise from electronically excited species generated during oxidative metabolic reactions, including ROS-mediated lipid peroxidation, these emissions may provide a sensitive optical correlate of tissue redox state[10]. In this context, Sefati et al., investigated whether hippocampal UPE intensity could distinguish normal, pathological, and treatment-responsive states in a streptozotocin (STZ)-induced rat model of sporadic AD[46]. They found that intracerebroventricular STZ significantly increased hippocampal UPE intensity, malondialdehyde (MDA) concentration, and acetylcholinesterase activity compared with control and sham groups, linking heightened photon emission to oxidative stress and cholinergic dysfunction. Treatment with donepezil reduced UPE intensity, MDA concentration, and AChE activity while improving memory performance, suggesting that UPE may track disease-associated oxidative injury and therapeutic response in this model[46].

These findings support the possibility that UPE could serve as an optical biomarker of oxidative and metabolic dysfunction in AD-relevant tissue states. However, the translational implications remain preliminary: the study used an experimentally induced rodent model, measured hippocampal emissions ex vivo, and proposed future photonic-chip approaches that have not yet been validated for clinical diagnosis or longitudinal monitoring in humans. This line of work is nonetheless conceptually important, as oxidative stress and metabolic dysregulation are increasingly recognized as early contributors to AD pathogenesis and may precede or interact with amyloid-β accumulation and plaque formation[45]. Thus, UPE-based approaches may eventually complement existing biomarker strategies by detecting redox and bioenergetic changes that occur early in neurodegenerative disease, but additional in vivo, longitudinal, and human studies are needed before UPE can be considered a diagnostic or therapeutic monitoring tool.

Given the central role of oxidative stress in neurodegenerative disease, Kurian et al. proposed a theoretical framework in which ROS-generated UPE may interact with neuronal microtubule networks[47]. As tubulin contains aromatic amino acids, particularly tryptophan and tyrosine, which

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absorb light in the ultraviolet range, the authors suggested that microtubules may be capable of absorbing and transferring photon energy through excitonic mechanisms. Prior in vitro studies cited in this work showed that exposure to exogenous ultraviolet photons can induce dose-dependent microtubule reorientation and reorganization, with maximal effects near ~280 nm, corresponding to the absorption range of tryptophan and tyrosine. Kurian et al. therefore hypothesized that ROS-derived UPE could stimulate excitonic energy transfer through microtubules, potentially contributing to intracellular energy redistribution, redox buffering, or signaling. However, this model remains speculative and should not yet be interpreted as evidence that microtubules serve as a validated UPE-based neural communication system in vivo. In tauopathic diseases, including AD and Parkinson's disease-related dementias, disruption of tau-microtubule stability could theoretically impair these proposed photonic transport properties, leading to altered photon handling and potentially worsening oxidative stress; this remains an important but unproven mechanistic hypothesis.

PBM offers a complementary, exogenous light-based approach that may converge on several molecular pathways also implicated in UPE biology. In preclinical models of AD, PBM has been associated with reduced amyloid-β burden, improved mitochondrial function, decreased oxidative stress and neuroinflammation, and improved cognitive performance, although study protocols vary substantially[48]. Human data remain early but encouraging. Systematic reviews and meta-analyses of human studies indicate that PBM is associated with modest improvement in global cognitive function and several specific domains such as executive function, with near-infrared PBM showing the strongest effects[49–51]. Thus, as in stroke, PBM in AD may act through mechanisms that overlap with those involved in UPE generation, particularly mitochondrial respiration, ROS modulation, oxidative stress, and cellular bioenergetics. Whether endogenous UPE can be used to predict, guide, or enhance PBM response in AD remains an open translational question. UPE.

3.3. Emerging Directions

3.3.1. Mental States & Anesthesia

Beyond acute injury and neurodegeneration, a smaller but intriguing body of work has examined UPE in relation to neurotransmission, emotional state, autonomic tone, and anesthesia, with possible future relevance to psychiatry and anesthesiology. The strongest mechanistic evidence comes from experimental studies showing that neurotransmitters can modulate UPE activity in neural tissue. Glutamate has been shown to induce sustained biophotonic activity in mouse brain slices, likely reflecting increased synaptic activity, oxidative metabolism, and ROS-linked photon generation[44]. Subsequent work suggested that acetylcholine, dopamine, norepinephrine, and GABA can enhance glutamate-induced UPE, whereas serotonin suppresses it; propofol also reduced both spontaneous and neurotransmitter-induced biophotonic activity[36,52]. These findings suggest that UPE is sensitive to neurotransmitter-dependent changes in neural metabolism and redox state, although current evidence does not support neurotransmitter-specific UPE "signatures." Rather, multiple neurotransmitter systems may converge on shared downstream pathways involving mitochondrial activity, oxidative metabolism, and ROS-mediated photon emission.

Autonomic state may also influence photon emission. In epinephrine-injected rats, UPE increased in association with changes in heart rate variability, suggesting that sympathetic activation and systemic arousal can modulate photon emission[53]. Together, these studies support the idea that UPE may reflect broader physiologic state changes, including neurotransmitter balance, metabolic demand, and autonomic tone. However, these relationships remain nonspecific, and the available data do not yet establish UPE as a diagnostic marker for specific neurologic or psychiatric disorders.

Human studies are more limited. Zapata et al. performed a proof-of-concept study in nine volunteers in whom upper-body UPE was measured during relaxed and anger-induced states[54]. UPE intensity was higher during anger than relaxation in all participants, suggesting that emotional arousal may alter spontaneous photon emission. However, the study was small, mood induction and

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mood measurement were subjective, and neurotransmitters or autonomic biomarkers were not directly measured. Therefore, these findings are best interpreted as preliminary evidence that emotional state and physiologic arousal may influence human UPE, rather than proof that UPE directly measures mood-specific neurotransmitter changes.

Anesthetic studies further suggest that UPE is modulated by state-altering drugs, but the direction of change appears agent-specific. In isolated rat brains, ketamine increased UPE while thiopental decreased it, despite both producing anesthesia[52]. These divergent effects likely reflect differences in pharmacology and metabolic state: ketamine's NMDA antagonism may increase glutamatergic turnover or oxidative-nitrosative activity, whereas thiopental may suppress global cerebral metabolism and excitatory neurotransmission. Propofol, as noted above, suppresses glutamate- and neuromodulator-induced UPE in brain slice experiments, consistent with its broader inhibitory effects on excitatory signaling and enhancement of GABAergic tone[36]. Collectively, these findings suggest that anesthetics influence UPE through heterogeneous effects on neurotransmission, mitochondrial metabolism, oxidative stress, and antioxidant capacity, rather than through a single consciousness-specific optical mechanism.

A more speculative literature proposes that microtubules may contribute to UPE generation, propagation, or anesthetic sensitivity. Theoretical models suggest that tubulin contains aromatic amino acid networks, especially tryptophan and tyrosine residues, that could absorb or transfer photon energy[12,22]. Related microtubule-based theories of consciousness, including the Orch-OR hypothesis proposed by Hameroff and Penrose, argue that microtubules may participate in conscious processing and may be susceptible to anesthetic effects through interactions with hydrophobic or aromatic regions of tubulin[55]. However, this framework remains controversial, and the current literature does not establish that UPE mediates consciousness or anesthetic action. At present, microtubule-photon models should be framed as hypothesis-generating rather than as validated mechanisms.

Exogenous light-based therapies provide a related but distinct clinical context. Bright light therapy, including white or blue-enriched light, is an established treatment for seasonal affective disorder and has shown benefit in major depressive disorder[56]. Its primary mechanism is thought to involve retinal photoreception, particularly intrinsically photosensitive retinal ganglion cells, with downstream effects on the suprachiasmatic nucleus, circadian regulation, and mood-regulating neural networks[57]. Red and near-infrared transcranial PBM has also shown positive effects in reducing depressive symptoms, self-reported anxiety, and OCD symptoms[58,59]. Green light therapy has demonstrated significant analgesic effects in animal models and early clinical studies of chronic pain. Its mechanism is thought to involve central opioid and endocannabinoid pathway modulation, anti-inflammatory effects, and visual-somatosensory circuit changes[60–62].

Taken together, the available evidence suggests that UPE is modulated by neurotransmitter activity, emotional arousal, autonomic tone, and anesthetic exposure, but these relationships are mechanistically heterogeneous and remain incompletely understood. Current findings are most consistent with UPE serving as a sensitive correlate of redox state, metabolic activity, and physiologic arousal rather than a specific readout of consciousness, mood, or individual neurotransmitter systems. Future studies combining UPE measurement with EEG, autonomic monitoring, neurochemical assays, and controlled anesthetic or psychiatric paradigms will be needed to clarify whether UPE can meaningfully inform the study of mental states, anesthetic depth, or therapeutic responses to light-based interventions.

3.3.2. Other Neurodegenerative Conditions

Multiple Sclerosis and Myelin Pathology

Demyelinating disease may represent a promising category for future investigation. Myelin has been proposed to act as a biological waveguide capable of channeling visible and near-infrared photons across axons based on evidence from experimental modeling and silver autography studies mentioned previously, showing UPE at the nodes of Ranvier dependent on activity[17,25,63,64]. If

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myelin is lost, such as in the case of multiple sclerosis, photon propagation and transmission may be altered, potentially changing UPE signatures. However, to date, there appear to be no well-validated studies directly measuring UPE in MS tissue, animal models of demyelination, or patients with demyelinating disease. Therefore, MS should be framed as a promising hypothesis-generating target rather than an established UPE application. Future studies could test whether demyelinated plaques, normal-appearing white matter, remyelinated lesions, or active inflammatory lesions differ in photon emission intensity, spectral profile, or activity-dependent UPE responses.

Parkinson's Disease and Melanin Photochemistry

Dopaminergic neurons contain abundant neuromelanin. UPE has been suggested by one study to accompany eumelamin and pheomelanin synthesis and degradation, especially via autooxidation of catecholamines, which produces numerous ROS intermediates such as hydrogen peroxide[65–68]. Given that PD involves neuromelanin-rich neurons, dopamine oxidation, mitochondrial impairment, and ROS generation, it is plausible that altered UPE could eventually be detected in PD-relevant tissue or models. However, this remains speculative: current evidence does not establish a PD-specific UPE signature, nor does it show that neuromelanin-derived photon emission can be measured in vivo as a biomarker of dopaminergic neurodegeneration. Future studies would need to compare UPE across dopaminergic neuron models, substantia nigra tissue, α-synuclein models, and neuromelanin-loaded cellular systems to determine whether UPE reflects dopamine oxidation, mitochondrial injury, inflammatory activation, or nonspecific oxidative stress.

Amyotrophic Lateral Sclerosis

ALS may represent another future application because the disease involves oxidative stress, mitochondrial dysfunction, glutamate excitotoxicity, neuroinflammation, impaired proteostasis, and cytoskeletal disruption, all of which could plausibly influence UPE generation[69–72]. However, no studies currently demonstrate UPE alterations in ALS tissue, patient-derived motor neurons, spinal cord samples, or animal models. Thus, ALS should be discussed as a rational future direction rather than an established application. Future experiments using SOD1, TDP-43, FUS, or C9orf72 models could determine whether UPE intensity or spectra correlate with mitochondrial stress, glutamate toxicity, axonal degeneration, or therapeutic response.

3.3.3. Cancers of the Nervous System

A substantial body of UPE research has emerged in oncology, where malignant cells and tissues often demonstrate altered photon emission compared with non-malignant controls. These differences are thought to reflect changes in oxidative metabolism, mitochondrial function, lipid peroxidation, membrane activity, and ROS-associated electronically excited species. This phenomenon has been demonstrated both in vitro and in vivo, with UPE profiles able to discriminate malignant from healthy tissue and even detect early malignancy in animal models and human samples[9,73–78].

Cancer is now understood as a multifactorial disease shaped by genetic, epigenetic, metabolic, immune, and microenvironmental alterations. Classical models emphasize oncogene activation, tumor suppressor loss, epigenetic drift, altered metabolism such as the Warburg effect, mitochondrial dysfunction, oxidative stress, and lipid peroxidation, all of which could plausibly contribute to altered UPE[9,79–82]. Alongside these canonical frameworks, a complementary biophysical perspective has also emerged. Levin and colleagues argue that bioelectric patterning in the form of resting membrane potentials, ion currents, and electrical fields act as an instructive layer of regulation that guides tissue organization[83–85]. Under this framework, cancer represents a breakdown of the same voltage-based patterning system that coordinates neural networks, and which has been shown to alter UPE. Levin's group has demonstrated that depolarized membrane potentials can induce tumor-like phenotypes even in the absence of genetic mutations and suppress oncogenesis in vivo by normalizing bioelectric states. This work supports the broader concept that cancer is not only a genetic disease but also a disorder of tissue-level organization and cell-state regulation. The

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relationship between bioelectric patterning and UPE remains speculative but conceptually relevant. If UPE reflects redox state, membrane activity, mitochondrial metabolism, or intercellular signaling, then tumor-associated changes in bioelectric organization could theoretically alter photon emission patterns. However, current evidence does not establish UPE as a direct readout of bioelectric patterning, nor does it show that UPE mediates oncogenesis. A more cautious interpretation is that UPE and bioelectricity may represent overlapping biophysical windows into altered cellular state, tissue organization, and metabolic stress.

Most UPE-oncology work to date has focused on non-CNS malignancies such as skin, breast, cervical, colorectal, and liver cancers, where malignant tissue has consistently shown a higher UPE intensity, altered spectra, and even detectability at premalignant stages. In contrast, data directly measuring UPE in nervous system cancers remain sparse. A recent neural cell culture study measured biophoton emissions from Neuro-2a cells and astrocytes and found that red and near-infrared light exposure could alter emission intensity in culture, including under oxidative or mitochondrial stress conditions[40]. Although Neuro-2a cells are neuroblastoma-derived, this work should be interpreted as preliminary neural-lineage cell culture evidence rather than a direct model of primary CNS malignancy. To our knowledge, systematic UPE measurements have not yet been reported in primary brain tumors such as glioblastoma, lower-grade glioma, meningioma, medulloblastoma, or primary CNS lymphoma. This represents an important gap and opportunity for future research. Future studies could compare UPE intensity, spectra, and temporal dynamics across tumor grade, hypoxic burden, necrosis, IDH mutation status, proliferative index, mitochondrial phenotype, and treatment response. Such work may clarify whether UPE can serve as a sensitive optical correlate of tumor metabolism, oxidative stress, or therapeutic response in nervous system cancers, while avoiding premature claims that it is currently a validated biomarker for CNS tumor diagnosis.

Representative disease-oriented studies are summarized in Table 2.

Table 2. Main Disease Focused Neural UPE Papers with Potential Future Clinical Relevance.

Title	Study	Experimental Model / Detection Method	Main UPE Finding	Proposed Clinical Relevance
Stroke / Ischemia				
In vivo imaging of spontaneous ultraweak photon emission from a rat's brain correlated with cerebral energy metabolism and oxidative stress	Kobayashi et al., 1999	In vivo rats; Photomultiplier tube (PMT) and EEG	Brain UPE decreased with ischemia/glucose deprivation and increased with hyperoxia.	Supports UPE as a potential marker of ischemic cerebral injury.
Biophoton imaging identification of delayed functional neural circuit injury after cerebral ischemia-reperfusion	Chai et al., 2021	Rat brain slices; Electron-measuring Charge Coupled Device (EM-CCD)	Glutamate-evoked biophotonic activity remained impaired despite apparent structural recovery after stroke.	Suggests UPE may detect persistent post-ischemic circuit dysfunction.
The effect of venous and arterial occlusion of the arm on changes in tissue hemodynamics, oxygenation, and ultra-weak photon emission	Scholkmann et al., 2013	Human forearm ischemia model; PMT and Near-Infrared Spectroscopy (NIRS)	UPE decreased during arterial occlusion and increased during reperfusion, correlating nonlinearly with tissue oxygenation metrics.	Supports UPE as a marker of ischemia, reperfusion, and slow oxidative metabolic dynamics associated with oxygenation status.
Alzheimer's Disease / Dementia / Aging				

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Monitoring Alzheimer's disease via ultraweak photon emission	Sefati et al., 2024	In vivo rat; PMT	Hippocampal UPE increased in AD-like rats and correlated with oxidative stress and lipid peroxidation, partially rescued by donepezil administration	Supports UPE as a potential biomarker of AD-related metabolic dysfunction and treatment response
Reduced biophotonic activities and spectral blueshift in Alzheimer's disease and vascular dementia models with cognitive impairment	Wang et al., 2023	Rat brain slices; EMCCD	Alzheimer's disease and Vascular dementia models showed reduced glutamate-induced UPE and a spectral blueshift, partially reversed by GluN2B antagonism.	Suggests altered glutamatergic and metabolic photonic responses may reflect synaptic dysfunction and impaired neural efficiency in neurodegeneration.
Spectral blueshift of biophotonic activity and transmission in the ageing mouse brain	Chen et al., 2020	Mouse brain slices; biophoton spectral analysis device (BSAD)	Aging was associated with spectral blueshift of glutamate-induced UPE.	Supports UPE spectral properties as potential markers of age-related metabolic decline, potentially similar to the blueshift observed in models of neurodegeneration.
Oxidative species-induced excitonic transport in tubulin aromatic networks: Potential implications for neurodegenerative disease	Kurian et al., 2017	Computational/theoretical modeling	Modeling suggested tau-related microtubule disruption may impair excitonic energy transfer within tubulin networks.	Theoretical framework linking oxidative stress, tau pathology, and altered UPE.
Anesthesia / Consciousness				
The impact of ketamine and thiopental anesthesia on ultraweak photon emission and oxidative-nitrosative stress in rat brains	Ghaffari et al., 2025	Isolated rat brains; PMT	Ketamine increased UPE while thiopental decreased it although both suppress neural activity.	Suggests anesthetics differentially alter UPE.
Biophotonic Activity and Transmission Mediated by Mutual Actions of Neurotransmitters are Involved in the Origin and Altered States of Consciousness	Chai et al., 2018	Mouse brain slices; EMCCD	Glutamate induced sustained UPE, while neurotransmitters differentially altered the signal: Acetylcholine enhanced activity, dopamine produced transient enhancement, and serotonin suppressed emission. Propofol dose-dependently inhibited glutamate-driven UPE and abolished neurotransmitter effects.	Suggests neurotransmitter balance and anesthetic state influence neural UPE.
Increased photon emission from the head while imagining light in the dark is correlated with changes in electroencephalographic power	Dotta et al., 2012	Human scalp PMT recordings and EEG	Visual imagery increased scalp UPE and correlated with EEG.	Suggests cognitive state may influence UPE emissions.

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Exploring ultraweak photon emissions as optical markers of brain activity	Casey et al., 2025	Human scalp PMT and EEG recordings	Scalp UPE exhibited slow oscillatory structure and task-dependent changes.	Suggests cognitive tasks may influence UPE emissions.

4. Discussion, Conclusions, & Future Directions

Taken together, the studies reviewed here suggest that UPE may serve as a reproducible optical correlate of how neural tissue couples metabolism, excitation, and cellular stress. Across experimental preparations and disease models, UPE in the nervous system appears to track changes in mitochondrial oxidative metabolism, ROS, membrane activity, and excitation-metabolism coupling. Depolarization, glutamatergic stimulation, ischemia-reperfusion, psychostimulant exposure, neurodegenerative pathology, anesthesia, autonomic arousal, and cognitive or mental-state paradigms have all been shown to alter UPE intensity, timing, or spectral properties in ways that broadly correspond to underlying biochemical and bioelectric changes.

At present, the strongest evidence supports UPE as a sensitive marker of mitochondrial redox status and oxidative stress, with an additional activity-dependent component in neural tissue. High extracellular potassium, glutamate, and methamphetamine increase UPE in brain slices or in vivo, whereas tetrodotoxin, metabolic inhibitors, calcium removal, and ischemia suppress it. Stroke models demonstrate reduced photon emission during ischemia, rebound increases with reperfusion and hyperoxia, and persistent depression of evoked UPE in injured but reperfused tissue. Glutamate-evoked biophotonic activity also appears to follow distinct initiation, maintenance, and rebound phases that depend differentially on action potentials, calcium influx, oxidative metabolism, and presynaptic vesicle cycling. These findings place UPE at the intersection of synaptic activity, bioenergetics, and redox biology.

In neurodegenerative disease models, particularly AD, UPE changes have been linked to altered NMDA receptor function, oxidative stress, mitochondrial dysfunction, lipid peroxidation, and microtubule-associated mechanisms. In oncology and neuro-oncology, UPE may reflect altered redox state, metabolic reprogramming, and tissue organization, although direct evidence in primary nervous system tumors remains limited. UPE has also been reported to change with anesthesia, neurotransmitter manipulation, autonomic tone, and emotional or cognitive states, suggesting that it may capture broader physiologic shifts in neural and systemic metabolism. However, these associations remain mechanistically heterogeneous and should not be interpreted as evidence that UPE provides a specific readout of any single neurotransmitter, disease state, or conscious experience.

It is therefore important to clarify what UPE currently is and is not. The available literature positions UPE as an optical readout of biochemical activity and excitation-metabolism coupling in the nervous system. It is not simply a “ROS meter,” because different stressors can produce distinct UPE patterns that do not always correspond linearly with bulk ATP or ROS assays. UPE is also not yet a validated functional signaling modality in vivo, although several hypotheses have proposed that photons may participate in axonal, microtubule-based, or intercellular communication. These models remain intriguing but speculative. Finally, UPE is not yet a clinically validated biomarker in neurology, psychiatry, oncology, or any other field of medicine. Rather, the current evidence identifies UPE as a promising experimental signal with multiple potential translational applications that require further validation.

Several methodological limitations currently constrain the field. Most two-dimensional UPE imaging systems require long integration times, low temporal resolution, and ex vivo or open-skull preparations, limiting their ability to capture rapid neural dynamics or to be applied in awake humans. Spectral resolution is often limited or absent, even though different photochemical pathways may occupy distinct wavelength ranges. Spatial localization in deep tissue is challenged by scattering, absorption, skull attenuation, and low photon flux. Experimentally, many paradigms lack simultaneous UPE measurement with electrophysiology, hemodynamics, calcium or voltage imaging, and molecular markers, making it difficult to disentangle neuronal, vascular, inflammatory,

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and metabolic contributions. Anesthesia, temperature, delayed luminescence from prior light exposure, tissue handling, and heterogeneous cellular composition are additional confounds. Biologically, multiple potential photon sources—including mitochondrial electron leak, lipid peroxidation, catecholamine oxidation, melanin chemistry, peroxisomal activity, and inflammatory-cell metabolism—make it difficult to map a given UPE change onto a single mechanism.

Within this context, several concrete avenues for future work emerge. Technologically, the field needs more sensitive, faster, and more spatially precise detection platforms, including optimized EMCCD, sCMOS, photomultiplier tube, and single-photon avalanche diode systems. Improved low-light imaging would allow UPE to be studied with better temporal resolution and under more physiologically relevant conditions. Parallel development of spectral UPE imaging, even with coarse wavelength separation, could improve mechanistic inference by distinguishing emission patterns associated with lipid peroxidation, excited carbonyl species, superoxide-related reactions, singlet oxygen, or other photochemical sources. For clinical translation, miniaturized shielded detectors and integration with existing neurophysiologic tools such as EEG, NIRS, and optical imaging may enable early-stage human studies. At the tissue level, silver autography and related histologic approaches could help localize UPE-associated activity with microscopic resolution, analogous to how voltage-sensitive dyes and calcium indicators advanced the study of bioelectric and neural activity.

Mechanistically, future studies should prioritize source attribution. Pharmacologic and genetic perturbations targeting mitochondrial complexes, lipid peroxidation, calcium handling, catecholamine synthesis, NADPH oxidase activity, inflammatory signaling, and antioxidant systems could help identify the dominant contributors to UPE under different conditions. Cell-specific approaches will also be essential. Neurons, astrocytes, microglia, oligodendrocytes, endothelial cells, tumor cells, and infiltrating immune cells may each generate or modulate UPE differently depending on metabolic state and disease context. In slice and in vivo preparations, combining UPE with patch-clamp recordings, calcium imaging, voltage imaging, ROS-sensitive probes, oxygen monitoring, perfusion imaging, and hemodynamic measures could clarify how UPE initiation, maintenance, and rebound phases align with synaptic, metabolic, and vascular events.

From a disease perspective, the most immediately promising translational targets are conditions in which redox imbalance, excitotoxicity, mitochondrial dysfunction, and metabolic failure are central to pathophysiology. In stroke, UPE could be correlated with perfusion imaging, EEG, structural MRI, histologic injury, and behavioral outcomes across ischemic, reperfusion, and recovery phases. Such studies could test whether UPE provides unique prognostic information about salvageable penumbra, reperfusion injury, delayed synaptic failure, or tissue recovery beyond conventional imaging and electrophysiology. In neurodegenerative disease, UPE may be useful for detecting early metabolic and oxidative changes that precede overt neuronal loss, although this will require longitudinal studies across disease models and, eventually, human tissue or patient-based paradigms.

Neuro-oncology represents another important but underexplored direction. Peripheral oncology studies suggest that malignant cells and tumor-bearing tissues can exhibit altered UPE intensity, spectra, and temporal dynamics, likely reflecting oxidative metabolism, lipid peroxidation, mitochondrial dysfunction, and altered tissue organization. Early neuro-oncology studies could begin with ex vivo measurements from freshly resected brain tumors and adjacent non-tumor tissue, testing whether gliomas, meningiomas, medulloblastomas, primary CNS lymphomas, or metastatic tumors show distinct UPE profiles. These studies could evaluate whether UPE varies by tumor grade, necrosis, hypoxia, IDH mutation status, proliferative index, metabolic phenotype, or treatment exposure. In vitro experiments comparing neural stem cells, neurons, astrocytes, microglia, glioma lines, neuroblastoma lines, and patient-derived tumor organoids under controlled ROS, oxygen, and membrane-potential manipulations could help bridge molecular mechanisms with broader bioelectric models of cancer.

A final cross-cutting opportunity lies at the intersection of endogenous UPE and exogenous PBM. Red and near-infrared light can modulate mitochondrial function, ROS production, inflammation, and cellular bioenergetics, and in some contexts can also alter UPE itself. Recent work

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in neural-lineage cell culture suggests that red and near-infrared light exposure can change biophoton emission under oxidative or mitochondrial stress, although these changes do not always map directly onto bulk ATP or ROS levels. Treating UPE and PBM as a bidirectional system—where metabolism generates photons and photons modulate metabolism—could create a powerful experimental framework. Controlled light stimuli could be used as perturbations while UPE, ROS, mitochondrial function, electrophysiology, and behavioral outcomes are measured in parallel. This approach may clarify when exogenous light simply shifts redox set points and when it might interact with more specific photonic or bioelectric signaling pathways.

Importantly, the relationship between endogenous UPE and PBM should be framed cautiously. Hamblin has argued that endogenous biophoton flux is unlikely to account for transcranial PBM effects because therapeutic light delivers photon fluxes many orders of magnitude greater than spontaneous UPE[85]. This is a valid critique of any claim that endogenous UPE directly mediates PBM-like effects. However, it does not exclude the possibility that UPE carries physiologically meaningful information, reflects the state of PBM-relevant molecular targets, or provides a readout of tissue responsiveness to light. Moreover, if intracellular photon production is substantially higher than extracellularly detected UPE, then measured emissions may underestimate the local photonic environment within cells[85]. This remains a testable hypothesis rather than an established mechanism.

In summary, current evidence positions UPE in the nervous system as a sensitive but nuanced optical marker of redox metabolism, mitochondrial function, and neuronal excitation. Whether photons themselves participate in neural communication or primarily represent byproducts of biochemical processes remains an open question. Resolving this will require more precise instrumentation, standardized protocols, spectral analysis, source-attribution experiments, and multimodal designs that link UPE to electrophysiology, metabolism, hemodynamics, molecular state, and behavior. If successful, these efforts could transform UPE from a biophysical curiosity into a useful biomarker of nervous system metabolic health and, in selected contexts, a potential guide for therapeutic intervention.

Looking ahead, the field would benefit from a coordinated effort to map the sources, spectra, dynamics, and functional consequences of UPE across tissues and disease states. Such a “photo-omic” framework, analogous in spirit to genome, proteome, metabolome, and connectome initiatives, could help define when UPE reflects nonspecific oxidative stress, when it provides disease-relevant information, and whether it ever participates in biologically meaningful signaling. The nervous system, with its high metabolic demand, complex bioelectric activity, diverse cellular architecture, and vulnerability to redox-mediated injury, is a compelling starting point for this effort.

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Abbreviations

The following abbreviations are used in this manuscript:

UPE	Ultraweak Photon Emission
PMT	Photomultiplier Tube
EMCCD	Electron-Multiplying Charge-Coupled Device
ROS	Reactive Oxygen Species
PBM	Photobiomodulation
PD	Parkinson's Disease
AD	Alzheimer's Disease
VaD	Vascular Dementia
ALS	Amyotrophic Lateral Sclerosis
MS	Multiple Sclerosis

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