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Review

Approaches to Monitor Circuit Disruption after Traumatic Brain Injury: Frontiers in Preclinical Research

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Abstract: Mild traumatic brain injury (TBI) often results in pathophysiological damage that can manifest as both acute and chronic neurological deficits. In an attempt to repair and reconnect disrupted circuits to compensate for loss of afferent and efferent connections, maladaptive circuitry is created and contributes to neurological deficits, including post-concussive symptoms. The TBI-induced pathology physically and metabolically changes the structure and function of neurons associated with behaviorally relevant circuit function. Complex neurological processing is governed, in part, by circuitry mediated by primary and modulatory neurotransmitter systems, where signaling is disrupted acutely and chronically after injury, and therefore serves as a primary target for treatment. Monitoring of neurotransmitter signaling in experimental models with technology empowered with improved temporal and spatial resolution is capable of recording in vivo extracellular neurotransmitter signaling in behaviorally relevant circuits. Here, we review preclinical evidence in TBI literature that implicates the role of neurotransmitter changes mediating circuit function that contributes to neurological deficits in the post-acute and chronic phases and methods developed for in vivo neurochemical monitoring. Coupling TBI models demonstrating chronic behavioral deficits with in vivo technologies capable of real-time monitoring of neurotransmitters provides an innovative approach to directly quantify and characterize neurotransmitter signaling as a universal consequence of TBI and the direct influence of pharmacological approaches on both behavior and signaling.

Keywords: traumatic brain injury; neurotransmitters; circuits; behavior; morbidity; electrochemistry; glutamate; dopamine; post-concussive symptoms; microbiota

1. Introduction: Acute Chronic Deficits of Mild TBI

Affecting over 2.5 million people across the United States, traumatic brain injury (TBI) is the leading cause of non-fatal injuries [1,2]. Over 75% of TBI patients that report to emergency departments are diagnosed with mild TBI. Mild TBI is defined as an acute brain injury as a result of mechanical energy to the head from external physical forces that cause a brief loss of consciousness and or alteration of mental state (Glasgow coma scale score 13–15 at 30 min after the impact) without loss of tissue [3].

Damage after TBI can be classified as focal or diffuse injury. Focal brain injuries often produce overt injuries such as skull fracture, intracerebral and subdural hematomas, subarachnoid hemorrhage

with significant elevations in intracranial pressure [4]. Diffuse TBI is the result of rapid rotational, and/or liner acceleration and deceleration forces cause widespread damage to the neuronal and vascular structures with no overt pathology identified by imaging studies [5]. Studies in humans and animals have shown neuronal pathology, microvascular disruption, white matter injury and axonal disconnection [6,7]. The biomechanical forces primarily cause metabolic dysregulation with imbalances in the ionic flux and disruption of the blood-brain barrier (BBB) that further exacerbate the damage [8–10]. The white matter injury resulting from axonal injury has the potential to disconnect neuron-specific relays between brain regions with implications for animal and patient behavioral morbidities. The diffuse axonal injury (DAI) is the earliest pathognomonic feature of mild TBI and is likely the key determinant of the long-term outcome [11]. The pathophysiological cascade involves secondary injuries that gradually evolves over seconds to months after primary injury. The secondary injuries involve metabolic and cellular derangements with neurometabolic cascades of unregulated neurotransmitter release (initiated by mechanical brain tissue deformation), increased oxidative stress, free radical production, inflammation and cell swelling [12–14] that exacerbate the primary injury and precipitates behavioral/mental deficits. These acute pathological perturbations are associated with early clinical characteristics of TBI with implications for long-lasting impairments [15]. Importantly, the heterogeneity and diversity in the pathogenesis of diffuse TBI by disrupting brain circuits emphasize the importance of considering the course and morbidity of injury.

Mild TBI cases (20–50%) develop persistent morbidities within one-month post-injury [16]. Patients often suffer transient symptoms that can persist months after initial injury with impaired brain function in cognitive, affective, somatic, and motor domains [17,18]. Neuropsychological tests in patients and neuropathological assessments in experimental TBI indicate continued posttraumatic symptoms that can persist for months to years after TBI [19–22] or late-onset symptoms of variable in duration with subjective symptomologies [23]. Post-concussive symptoms (PCSs) involve common constellation of symptoms reported by patients after mild-to-moderate TBI. PCSs have been previously diagnosed based on the International Classification of Diseases (ICD)-10, or based Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria as symptoms and problems in three or more multiple domains involving (1) headache, dizziness, general malaise and excessive fatigue, (2) mood and emotional changes such as irritability, depression and/or anxiety, (3) lack of concentration and memory deficits; and (4) fear of permanent brain damage [24]. It is estimated that 5.3 million survivors currently live with PCSs, which contribute to the disability-adjusted life years, impairment of activities in daily living, impede or can complicate return to the work [25,26]. The underlying mechanisms of persisting and emerging PCSs likely arise as a consequence of impaired activation and function of brain circuitry that occurs in response to adaptive or maladaptive compensation. From this perspective, the theme of circuit disruption has emerged as a potential explanation for many of the observed PCSs. The development of PCSs is also influenced by several factors including, but not limited to, personality, mental health, physical health, social status, gender, nutrition, alcohol, and substance use, that also may affect the rate of recovery after injury [27–29]. Together, these pre-injury conditions influence a patient's recovery and prognosis.

Although diffuse white matter disconnections are a characteristic, multicentric outcome of the mechanical impact of TBI, the neurological impairment may reflect dysfunction rather than just neuronal damage. The initial injury and subsequent injury cascade influence the functional state of surviving neurons, astrocytes and microglia and compensatory alterations involving multiple neurotransmitter systems that lead to synaptic deficits that lead to deficits in circuit function. Insights into the neuronal circuits reveal anatomically unique changes in several neurotransmitter systems that modify neuronal dynamics, synaptic function, receptors and transporters [15,30,31]. Our understanding of the development of morbidity and targets for recovery is likely to be informed by studying a variety of neurotransmitter signaling through the application of electrochemical techniques.

2. Current Animal Models of TBI

Research into the pathology and pathophysiology of TBI has been rapidly advanced by the development of animal models. So far, the animal models replicate injury types, providing a better understanding of molecular and cellular mechanisms, neurological deficits along with possible rehabilitative/neuroprotective strategies. Rodent and non-human primate TBI models simplify the complex events observed in humans while consistently and robustly reproducing the primary and secondary injuries. In addition, TBI models have provided the opportunity to evaluate for translatable biomarkers that can track TBI progression in humans.

For direct clinical relevance to diffuse TBI, several diffuse models of injury including fluid percussion, weight-drop, and blast injury models have been developed and modified to provide a preclinical platform recapitulating features of human TBI condition. The fluid percussion injury (FPI) imparts a fluid pressure pulse to the intact dura through a craniotomy which can be located laterally or centrally over the brain (for a diffuse or mixed pathology). The pressure pulse is a variable that can be controlled to alter injury severity. Midline (or central) FPI is predominantly used to produce DAI, petechial hemorrhage, and white matter damage in both hemispheres [32]. In relevance to human TBI, the midline FPI model in rodents has been invaluable in studying the longitudinal pathophysiology of diffuse brain injury. The plethora of information derived from the FPI model has shed light on the pathology involving neurophysiology, neuropathology, neuroimaging and behavioral manifestations that are relevant to clinical consequences [33–35]. The weight-drop injury model induces impact acceleration with a falling guided weight on the skull, with or without craniotomy. The severity of the injury can be adjusted by changing the mass of the weight and height drop. Besides widespread DAI, the model induces bilateral neuronal damage with the appearance of petechial hemorrhage that closely mimics human TBI [36]. The blast TBI model is simulated using explosives, compressed air, and gas in either blast or shock tubes to mimic the blast injuries commonly observed among military service members. The model employs a compression-driven shock tube to induce blast wave creating a series of effects involving diffuse cerebral edema, hyperemia, and vasospasm [37,38].

Behavioral alterations have been observed in most of the TBI animal models and characterization of behavioral assays is essential for understanding neural systems influencing the behavioral phenotype. As a valuable read-out to probe detailed mechanisms of functions and dysfunctions, various behavioral paradigms help characterize the behavioral repertoire similar to the acute and chronic sequelae that TBI survivors suffer. The assays provide for the sensitive, objective, and quantifiable behavioral measures with the use of video tracking, automated recordings, and detection technologies to record and analyze the behaviors. The assays include neurobehavioral assessment [39], exploratory behavior [40,41], learning and memory [42], and sensory sensitivity [43,44]. These behavioral models have a high degree of face validity, wherein the observable phenotype in the animal reproduces the human TBI condition.

3. Circuit Dysfunction after Diffuse TBI: Adaptive and Maladaptive Responses

Animal models have extended clinical findings to show impaired neuroplasticity after diffuse TBI [45]. Neural plasticity is highly adaptive and works to maintain the homeostatic processes by recruiting neurotrophic factors which compensate for the injury-induced adaptations [46,47]. Diffuse TBI initiates a widespread regenerative counter-response that includes reconnection of surviving neurons [48] and collateral sprouting of remaining axons near the denervated regions to create new contacts [47]. Changes in glia and vasculature contribute to the generation of new connections [49,50], where maladaptive reorganization may compound the degree of functional compromise while the injured brain attempts to restore the lost function [51,52]. Yet, it is not well understood the extent to which plasticity is maladaptive and instigates faulty reverberations within circuitry that can have mixed functional outcomes [47]. Indeed, surviving neurons are under metabolic stress and are overwhelmed with increased pathological burden. The ongoing reorganizational processes likely contribute to the observations of late-onset behavioral deficits. Thus, it is reasonable to predict that behavioral morbidities underlying PCSs arise as a consequence of multi-level adjustments that

occur over time post-injury as a result of cellular modifications, alterations in neurotransmission and circuit reorganization.

4. TBI-Induced Changes in Neurotransmitter Signaling: Acute and Chronic Responses to TBI

Dysregulation of the neurotransmitter systems has been associated with several neurodegenerative diseases as well as neuropsychiatric disorders. Alterations in neurotransmitters after TBI leads to compensatory alterations in neurotransmitter receptors and related signaling pathways, important for circuit-level information transmission. The function of brain circuits is governed, in part, by several neurotransmitter systems that regulate neuronal information flow through exocytosis, uptake and recycling events.

4.1. Primary Neurotransmitters

4.1.1. Glutamate

Glutamate is the primary excitatory neurotransmitter and more commonly implicated in TBI neuronal susceptibility to excitotoxic injury [53]. Released into the extracellular space through deformation-induced depolarization, stimulation, or exocytosis of synaptic vesicles, glutamate controls circuit function spanning a wide range of spatio-temporal scales. The clearance of glutamate from the extracellular space is regulated by high-affinity, sodium-dependent excitatory-amino-acid transporters (EAATs) on astrocytes, primarily EAAT2 (GLT-1 in rodents) and EAAT1 (GLAST in rodents) [54,55]. Further, damage to vasculature can cause platelet activation that releases glutamate that can permeate the BBB increasing extracellular glutamate [56,57]. Increased extracellular levels of glutamate binds metabolic glutamate receptors that can mediate neuronal damage through secondary injury processes and exacerbating existing neuronal pathology [58,59].

Several studies demonstrate significant glutamate dysregulation as an instigator of acute pathophysiology in days following TBI. Clinical microdialysis studies demonstrate increased extracellular glutamate levels as early as 24 h post-injury and up to 9 days post-injury [60–62]. Focal and diffuse TBI rodent models have demonstrated increased extracellular glutamate levels as early as 1 h post-injury [63,64]. TBI-induced increases in extracellular glutamate alter the localization of glutamate receptors and transporters, further impairing extracellular regulation of glutamate, reducing glutamate buffering capacity and reuptake patterns that modulate synaptic signaling [65]. Prolonged activation of NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors can induce neurodegeneration linked to the loss of membrane potential and enhanced cytosolic calcium levels after brain injury [66]. While excess glutamate can exacerbate apoptosis or necrosis in damaged neurons, the ability of astrocytes to rapidly and efficiently clear extracellular glutamate levels might be neuroprotective [54] and the extent of neuronal loss from excitotoxicity remains controversial.

4.1.2. GABA (γ-Aminobutyric Acid)

CABA (γ-aminobutyric acid), the main inhibitory CNS (central nervous system) neurotransmitter, is synthesized in inhibitory neurons from glutamate. While also being vulnerable to structural damage, it is also subject to homeostatic derangement following TBI. GABAergic neurons drive inhibitory elements of brain circuitry that shape circuit function through local and projection neurons. The released GABA acts on ionotropic $GABA_A$ and $GABA_B$ receptors located on the axonal terminals GABAergic transmission is terminated by clearance from the extracellular space by GABA transporters (GATs) on surrounding neurons and glia. GABA receptors regulate information processing with high physiological relevance through the maintenance of phasic and tonic inhibition, and modulation of neuronal excitability [67]. Experimental data have indicated that TBI can cause reduced expression of GAT at 24 h post-injury [68]. Magnetic resonance spectroscopy (MRI) has shown lower GABA levels in the prefrontal cortex associated with memory deficits in professional boxers repetitive mild

TBI [69]. Utilizing this technique, recent work has indicated region and time-specific changes in the GABA showing reduced levels in the cerebral cortex at 72 h and two-week post-mild TBI [70]. In the same region, increased $GABA_B$ receptor-mediated inhibition has been associated with loss of synaptic plasticity after sports concussion [71,72]. Acutely following TBI, changes in the $GABA_A$ expression alters phasic inhibition important for timing-based signaling leading to overexcitation of neurons and membrane depolarization. However, changes in GABA neurotransmission acutely and chronically offset the balance of excitation and inhibition that underlies several neurological diseases. Recently, electrochemical methods to record near real-time neurotransmission of GABA have been developed and open a wealth of opportunity to understand the role of GABA neurotransmission in the contribution to PCSs [73,74].

Glutamate and GABA are responsible for maintaining the excitatory–inhibitory balance required for circuit function. Post-traumatic epilepsy (PTE), a major long-term consequence of TBI, occurs as a result of a shift in the excitation-inhibition balance of the brain circuitry [53]. Anti-epileptic medications seek to restore the excitatory–inhibitory balance for the successful management of seizures. While PTE is most commonly associated with an imbalance in glutamate and GABA, it is important to consider that the excitatory–inhibitory balance is either directly and/or indirectly implicated with all symptoms associated with TBI as evidenced by the numerous types and distribution of transporters and receptors throughout the brain. Ongoing research is necessary to understand time- and region-dependent disruptions of this balance for improved treatment and management of side effects.

4.2. Modulatory Neurotransmitters

4.2.1. Dopamine

Accumulating evidence suggests that the catecholaminergic system is highly vulnerable to the effects of TBI. The monoamine neurotransmitter, dopamine (DA), modulates brain function via widespread DA efferent projections. The majority of DA neuron cell bodies are located in the midbrain (substantia nigra, ventral tegmental area), olfactory bulb, and hypothalamus. Midbrain DA neurons have a long and diffuse projection pattern that exposes DA neurons to shearing forces of injury, oxidative stress, impaired plasticity, and neuroinflammation (reviewed in [75]). The dopamine transporter (DAT) regulates the duration of DA in the extracellular space by clearing released DA through presynaptic reuptake [76]. DA plays an important role in cognitive, motor, emotional, motivational, and neuroendocrine processing from disruptions in the striatum, limbic system and frontal cortex [77,78].

Clinical studies implicate a disruption in DA neurotransmission over time post-injury. A computed tomography imaging study in humans has shown reduced striatal DA transporters (DAT) in the striatum after 142 days post-TBI [79]. This could lead to sustained increases of DA levels in the synaptic cleft that can be oxidized to form a quinone moiety that is capable of damaging cellular macromolecules through oxidative stress [80]. Diffusion MRI studies in moderate-severe brain-injured patients displayed reduced substantia nigra volume, and striatal DAT levels associated with cognitive deficits in information processing speed and executive functions [81], with the potential to influence symptoms associated with attention-deficit/hyperactivity disorder (ADHD), Parkinson's disease (PD) and Huntington's disease (HD).

Experimental models likewise suggest substantia nigra damage and remote cortical deficits due to damage of long-range axon projections [82]. The nigrostriatal dopaminergic axons have little to no myelin and are therefore more vulnerable to the shearing forces of TBI [83]. TBI augments DA levels and the rate of DA turnover (i.e., the ratio of DA metabolites to DA) at 1 h post-injury, indicating acute changes DA regulation [84]. Tyrosine hydroxylase (TH) is the rate-limiting enzymatic step for DA synthesis. TH and tissue levels of DA were increased in the prefrontal cortex out to 14 days following controlled cortical impact (focal injury) [85]. Moreover, fast-scan cyclic voltammetry (FSCV) measurements of DA neurotransmission have revealed reduced DA release and reuptake in dorsal

striatum after 2 weeks of controlled cortical impact injury [86]. Similar to clinical reports, reduced striatal DAT expression has been reported preclinically after focal TBI [87]. The DA projections are highly branched and contain several neurotransmitter release sites. Midline FPI induced extensive DA axonal pathology in medial forebrain (at 1 day post-injury) and enhanced pro-inflammatory cytokines in the striatum (at 6 h post-injury) that is implicated in reducing DA release [88]. Whole tissue HPLC analysis indicated augmented DA turnover with altered DA utilization in rat brain substantia nigra pars compacta after 28 days post-TBI [82].

Although the cognitive problems associated with TBI is multifactorial, a wide range of reports implicate that the disruption to the dopaminergic (DAergic) neurotransmission as an important factor [89–91]. A broad range of cognitive domains commonly affected after TBI including memory, learning, impaired attention including defects in sustained attention, information processing speed, and executive functions such as working memory, problem solving, planning, and impulse control. Importantly, treatment approaches for cognitive enhancement crucially depend on the DAergic level since the synaptic levels of DA are non-linearly associated with cognitive function [92].

4.2.2. Norepinephrine

Norepinephrine (NE), also known as noradrenaline, a catecholamine derived from I-tyrosine, has been implicated in the acute and chronic effects of brain injury [93,94]. Most of the experimental TBI studies report inconsistent alterations in levels of NE [85,95]. Time and region-dependent changes in NE turnover were observed after focal TBI with the contralateral reduction in the cerebral cortex and cerebellum after 6 h followed by a bilateral reduction in the hypothalamus, cerebellum, locus coeruleus and medulla at 24 h post-injury [96,97]. However, findings with whole tissue HPLC analysis show an acute increase in NE turnover (30 min post-focal lesion) in the somatosensory cortex [98] and chronic reduction persisted until 8 weeks post-injury [99]. Specifically, NE has been shown to influence processing speed via its alpha-2A receptor that functions to enhance excitability on target neurons [100,101]. At the higher-order connectivity level, NE modulates intrinsic networks, specifically the cognitive (salience) network, dysfunction of which produces impairments of cognitive control following TBI [102]. Treatment of NE dysregulation is considered with patients diagnosed with ADHD, PTSD, and depression.

4.2.3. Acetylcholine

Acetylcholine (ACh) is a fast-acting neurotransmitter of the cholinergic system that alters neuronal excitability, where changes in signaling have consequences linked to attention, drug abuse and food intake [103]. Clinical studies on the neuropathological, electrophysiological and pharmacological dynamics of ACh have provided evidence for cholinergic dysfunction after TBI [104]. Although clinical reports are scant, initial studies in TBI patients have demonstrated altered cerebrospinal fluid cholinergic function with reduced cholinesterase activity [105–107]. Increased levels of basal ACh and reduced activity of choline acetyl transferase (ChAT), a constitutive component of cholinergic nerve terminals have also been identified in cerebrospinal fluid of brain-injured rats [108,109]. Postmortem brain samples from patients who died as a result of head injury showed reduced ChAT activity [110], suggesting a decrease in the activity of cholinergic input. Clinical studies indicate that cholinergic drugs have been successfully prescribed for TBI patients with post-traumatic cognitive deficits [111,112]. Despite limited clinical data available in this regard, these findings suggest deficiencies in ACh innervation and synaptic activity after TBI. Loss of cholinergic neurotransmission is also a correlate of AD severity, and the overlapping pathology may be involved with TBI being a risk factor for AD-related disease progression [113,114].

Animal studies have shown acute effects of FPI on increased hippocampal ACh levels [115]. Phosphoryl [^{2} H_9] choline infusion measurements revealed that TBI alters ACh turnover in the rat midbrain at 12 min and 4 h after moderate FPI, indicating enhanced cholinergic transmission [116]. Cognitive impairments are the most common long-term deficits after TBI persisting for several years after

the injury. Regulation of attention, memory, and executive functions constitute significant components of the cortical cholinergic system that are disrupted after TBI [117,118]. Experimental reports have linked impaired cognition after TBI to chronic changes in cholinergic neurotransmission suggesting reduced ChAT in limbic brain regions [119]. It has been previously demonstrated that controlled cortical impact-induced focal brain injury causes significant reduction in hippocampal high-affinity [^{3}H] choline uptake thus suggesting that the cholinergic dysfunction is mainly associated with lower ability of cholinergic neurons to clear extracellular choline [120]. In vivo microdialysis technique has shown muscarinic antagonist evoked lower concentrations of ACh release in hippocampus and neocortex associated with spatial memory deficits among rats after controlled cortical impact brain injury [121,122]. At chronic time-point, post-controlled cortical impact, decreased ACh evoked release was associated with persistent cognitive deficits using microdialysis freely-moving behaving animals [123]. Other findings support that TBI-induced loss of ChAT was associated with cholinergic dysregulation [124]. There is also evidence that the compensatory response to TBI involves alterations in vesicular transporter for ACh (responsible for the concentration of ACh within synaptic vesicles) and mediator of cholinergic signaling showing increased expression of hippocampal vesicular ACh transporter (VAChT) at 4 weeks post-injury [125] and reduced muscarinic autoreceptor subtype 2 (M2) immunoreactivity [126].

4.2.4. Serotonin (5-Hydroxytryptamine, 5-HT)

Serotonin (5-hydroxytryptamine, 5-HT) is involved in the regulation of mood, where dysregulation of 5-HT neurotransmission plays a crucial role in neuropsychiatric disorders in the general population and TBI patients [127]. Moderate FPI in rats have shown to enhance levels of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) during the first 10 min after TBI [128]. However, the metabolite 5-HIAA extracellular levels were decreased initially during the first 10 min after diffuse TBI. Recent findings reveal that TBI reduces reuptake of 5-HT via modulation of the serotonin transporter (SERT) to prevent replenish of neuronal stores of 5-HT and consequently serotonergic transmission [129]. It has been shown that TBI-induced neuroinflammation decreases serotonin/tryptophan ratio at 21 days post-injury [130]. Overall, preclinical evidence suggests that 5-HT neurotransmission is decreased over time, contributing to the manifestation or worsening of neuropsychological symptoms.

The chronic consequences of TBI on psychiatric health have been identified not only after severe injury but also in several cases classified as mild to moderate. Psychiatric problems can be a major clinical problem as it potentially interferes with rehabilitation and overall recovery. The 5-HT system has wide distribution throughout the brain regulating various behavioral processes [131]. Over one-third of TBI patients develop major depression with increased risk linked to injury severity [132]. Selective serotonin reuptake inhibitors (SSRIs) are currently the first-line treatment for PTSD, depression, anxiety, and other mood disorders following TBI [133]. SSRIs are also used in the management of AD, PD, HD, and epilepsy. However, the relationship between this treatment and TBI is still under consideration.

4.3. Conclusion

There is growing evidence that changes in neurotransmission associated with TBI can instigate, accelerate, or exacerbate symptoms associated with chronic traumatic encephalopathy, epilepsy, PD, AD (and other forms of dementia), amyotrophic lateral sclerosis, HD, PTSD, ADHD, anxiety disorders, and depression disorders [134,135]. Modulation of primary and modulatory neurotransmission is primarily targeted for therapy. Yet the etiology of circuit dysregulation is still poorly understood. Progress in diagnosis and treatment of TBI is accounted for by growing acknowledgment that TBI is a neurological disease process rather than a single event that is a risk factor for several neurological disorders and diseases.

5. Biosensors for In Vivo Neurotransmitter Monitoring

Studies evaluating the extracellular dynamics of neurotransmitters can provide critical information regarding neuronal communication that is disrupted after TBI. Insight may be gained into aspects of functional neuronal communication by evaluating region-dependent pre-synaptic release, extracellular clearance, basal concentrations in anesthetized animals and behaviorally relevant signaling in freely-moving animals. Several techniques have been developed and applied for in vivo measurement of neurotransmission in various brain disorders. The functional role for neurotransmitter release events in the regulation of homeostasis, as well as influence on behaviors, have been previously reported. The use of cell-based fluorescent sensors [136], microdialysis [137] and fast-scan cyclic voltammetry [138] have been employed to probe changes in neurotransmitter signaling in naïve and models of neurological deficits. However, the development of devices with improved spatial and temporal resolution has helped capture endogenous, micromolar alterations to neurotransmitter release and reuptake.

Electrochemical detection with biosensors allows for real-time observation and quantification of neurotransmitter events. Biosensors often use a biological element (enzyme) to bind a specific analyte of interest and through the application of current, can detect and quantify the extracellular levels and kinetics of release and clearance at 2–100 Hz. The size of the sensors has also been decreased and in some instances, consists of several microsensors on a single electrode. Application of various exclusion layers to the microsensors during the fabrication process allows for increased selectivity, to avoid recording endogenous electroactive molecules that can prevent the detection of the analyte of interest. In vitro calibration allows for calculations where the current generated with applied potential is proportional to the analyte concentration. Electrochemical biosensor design continues to evolve with the recent implementation of thin needle-type probes that improve spatial resolution within subregions and small nuclei. The enzyme-modified electrodes and fast-scanning cyclic voltammetry behave been notably employed for spatial monitoring of rapid neurotransmitter dynamics. Fast-scanning cyclic voltammetry applies a triangular voltage wave to a carbon fiber electrode at high scan rates (300 V s^{-1}). The microelectrode measures the current as cyclic voltammogram as a characteristic oxidation and reduction peaks by subtracting the large background current. Other biosensors use enzyme-based microelectrodes with amperometric detection that provides the advantage of better resolution and minimal invasion/tissue damage [139]. The application of constant potential oxidizes or reduces the analyte of interest depending on intrinsic electrochemical properties to detect current that is linear to the electroactive activity in the biological tissue surrounding the microelectrode [140]. While most traditional neurotransmitters follow basic Michaelis-Menten kinetic predictions, non-classical functions can also occur, including spontaneous events, quasi-paracrine action, extrasynaptic overflow, transporter, receptor and channel-mediated release [141–143]. These non-classical and subtle changes associated with chemical transmission require novel approaches to data analysis and systematic neuropharmacological challenges to improve associations with behavioral relevance. Albeit, the evolution in technology allows for minimally invasive approaches to directly monitor and manipulate neurochemical transmission that measures fast fluctuating transients (quantity, timing, and dynamics) in spatially discrete relays of behaviorally relevant circuitry.

6. Brain-Injured Circuitry and Behavioral Morbidities: The Whisker Barrel Circuit

Diffuse TBI pathology is widespread, resulting in molecular, structural and functional alterations throughout the neuroanatomy that results in disrupted circuit function. At the basis of the pathology are the primary and secondary insults to neural circuits that determine the observed behavioral output. Thus, evaluation of these their anatomical connections is essential to understand how TBI-induced pathology alters functionality. One example of this is highlighted in the somatosensory thalamocortical circuit of the whisker barrel circuit (WBC) in rats. The somatosensory WBC in rodents processes sensory information from the mystacial whiskers for assessing spatial and textural information through thalamocortical and corticothalamic circuitry [144]. Whisker somatosensation represents the primary

sensory modality of rodents and is represented by a large portion of the brain for processing, similar to that of touch, sight, and hearing in humans. Each whisker is primed for sensory integration, consisting of large follicles with multiple superficial and deep vibrissal nerves associated with somatotopically distinct trigeminal neuron projections [145]. Trigeminal neurons project to the primary sensory nucleus (PrV), to the barreloids of ventral posterior medial (VPM) nucleus of the thalamus, to the primary somatosensory cortex forming discrete clusters in layer 4 (S1BF), which form the basis of the 'barrel' fields [146–150]. The somatotopographical localization of each whisker makes the WBC valuable to study circuit reorganization as evidenced by its history of use to study neuroplasticity in response to peripheral nerve injury, developmental patterning, neural coding, and neural computation [151–153]. As rodents largely rely on whisker function for environmental exploration due to poor eyesight, this circuit provides an ideal model to assess TBI-induced longitudinal circuit disruption followed by compensatory events that manifest in behavioral morbidity.

As observed by Thomas et al., TBI-induced pathology in the VPM and S1BF results in maladaptive circuit regeneration resulting in the development of late-onset, persistent sensory sensitivity to whisker stimulation during the whisker nuisance task (WNT) [44,154,155]. The WNT evaluates the behavioral response of the rat to tactile stimulation through three consecutive 5 min bouts of manual whisker stimulation. Naïve and uninjured sham rats are ambivalent to the stimulation, whereas TBI results in increased avoidance, evasiveness, and aggressiveness that is significant by 4 weeks and maintained to 8 weeks post-injury [154]. Hypersensitivity to whisker stimulation is exacerbated by elevated intracranial pressure (ICP) following FPI concurrent with neuronal somatic membrane damage and poration [156,157]. The WNT has been a reproducible approach to measuring circuit abnormalities across laboratories [154], injury models [158], and rodent species [159]. TBI-induced sensory hypersensitivity observed in the WNT can be likened to visual and auditory hypersensitivity commonly experienced by brain injury survivors [160,161], serving as an excellent in vivo model to longitudinally assess how maladaptive circuit reorganization after TBI leads to late-onset behavior morbidity.

The use of whisker barrel circuit serves as an ideal model to study TBI-induced neurotransmission in a behaviorally relevant circuit, showing hypersensitive glutamate signaling to be associated with the severity of response to the WNT [44]. Electrochemistry using glutamate selective MEAs were used to record real-time potassium (KCl)-evoked glutamate release within relays of the whisker barrel circuit (a glutamatergic circuit) after moderate severity FPI in anesthetized animals [162,163]. Local application isotonic KCl solution depolarized synaptic terminals near the microelectrode, evoking the release of glutamate. Evoked glutamate concentrations in the S1BF and VPM thalamus was significantly increased by 28 days post-injury, with robust responses in the dorsal and medial VPM. Glutamate clearance kinetics and glutamate transporter gene expression were similar between sham and 28 day FPI rats, indicating that increased KCl-evoked glutamate release was not a result of slower glutamate clearance from the extracellular space. Furthermore, KCl-evoked release in injured animals was more sensitive to ω-conotoxin, a voltage-gated calcium channel inhibitor, indicating that increases in KCl-evoked glutamate release were presynaptic in origin. VPM (and S1BF) responses correlate with the severity of sensory hypersensitivity evaluated by the WNT, indicating that changes in circuit function are impacting behavioral responses [44]. This study highlights how in vivo electrochemistry can be used to isolate aspects of neurotransmission relevant to behavioral morbidity, but it is also limited by evaluation in an anesthetized animal. While a presynaptic mechanism is implied, replicating these studies in awake behaving rats can provide behaviorally induced glutamate signaling that will provide additional information regarding how the signaling changes (increased bouts of released glutamate, increase concentrations, oscillatory signaling, etc).

Previously, studies on the contribution of circuit dysfunction to post-traumatic morbidity, in the form of neurotransmission, have relied on measurements obtained by microdialysis techniques. Microdialysis involves implantation of a probe with a 1–2 mm (for rats and mice) semi-permeable membrane for diffusion of extracellular neurotransmitters in artificial cerebral spinal fluid that is collected and assessed using HPLC. The probe and cannula implantation cause tissue damage

300–500 µm away for the probe [164]. Neurotransmitters are typically tightly regulated producing short fluxes of extracellular concentrations. Each sample is collected every 1–10 min, which does not accommodate the detection of the rapid release and uptake of many neurotransmitters [165,166]. The larger diameter (150 to 400 um) of the dialysis probe and constant infusion with artificial CSF can result in neurotransmitter dilution in the sampled region [167]. Microdialysis provides information on multiple neurotransmitters and their metabolites, peptides, and hormones in freely-moving animals, having many advantages along with these disadvantages highlighted here (reviewed in [168]). Recent advances using the genetically encoded neural activity indicators and two-photon imaging methods provide for non-invasive visualization of neurotransmitter release and neuronal activity [169,170]. Further, the microdialysis technique has been used in human patients to assess the amino acid concentrations in the brain following trauma [171]. However, these techniques lack information on the quantity of neurotransmitters in the extracellular space, particularly the dynamics of neurotransmitter clearance that shape the amplitude and duration of postsynaptic responses. Electrochemical biosensors have addressed temporal dynamics, improved spatial resolution, decreased tissue damage (in comparison with microdialysis), and the ability to evaluate near real-time dynamics of neurotransmitter release and clearance, while sacrificing the ability to evaluate multiple targets [137,172,173].

7. Electrochemical Biosensors for In Vivo Monitoring of Neurochemical Signaling

During the decades that neurochemical measurements largely relied on microdialysis, parallel developments were made on methods to measure at second and sub-second timescale with improved resolution. The developments were necessary since the cascade of events that follow signal transduction in neurotransmitter signaling involves a vast range of spatial and temporal scales. Initially, the microelectrodes developed were carbon-fiber based with low reproducibility and not suitable to measure molecules that could not be oxidized or reduced, like glutamate, GABA and ACh. Progress in technical advances over the past several years in microfabrication methods to create electrochemical biosensors containing more than a single microelectrode (microelectrode arrays; MEAs) have increasingly shown to be effective tools for neurotransmission detection. MEAs have served as an interface to develop amperometric enzyme-based biosensors for measurements of neurotransmitters, including electroactive and non-electroactive neurotransmitters in the extracellular space of the brain [174]. There are several unique types of MEAs currently being used to assess neurochemical signaling—varying in size, number of arrays, material, etc. [175–177]. Incorporation of multiple sensors allows for improved spatial resolution (in microns) and minimal tissue damage to the surrounding parenchyma [178,179]. The enzymatic biosensors have found wide applicability in brain research with amperometric biosensor recordings. The enzyme-based microelectrode arrays offer a better utility tool to monitor chemical signaling, they overcome the limitations associated with low temporal resolution and provide continuous in vivo monitoring at higher sampling rates. Their low limit of detection provides for near real-time measurement of chemical signaling involving synaptic events and neurotransmitter overflow. MEA coupled with amperometry has been employed to measure glutamate, GABA [74], adenosine [180], ACh [181], lactate [182] and glucose [183]. The non-electroactive neurochemicals are detected by immobilizing oxidase enzymes in a suitable polymeric film onto the electrode surface combined with the amperometric detection of hydrogen peroxide as a reporter molecule. Platinum or its alloys are commonly used as electrode recording surface materials due to their excellent electrocatalytic activity [184]. Importantly, in vivo biosensing has been achieved by polymer modification by enzyme immobilization using glutaraldehyde in the presence of bovine serum albumin onto the surface of microelectrodes [185]. The MEA has been employed to monitor transient changes in extracellular glutamate in animal models of Alzheimer's disease [186], epilepsy [187], stress [188], aging [189] and TBI [44,162,190]. Miniaturization of MEAs enables stereotaxical lowering into discrete anatomical regions of interest and allows long-term neurotransmitter recordings. A limitation of MEAs is that they can lose sensitivity due to loss of an exclusion layer. Yet detection of this loss is immediate and

therefore does not impede interpretation of the data. Depending on the design of the MEA, they are also restricted in the number of extracellular analytes they can measure in comparison to microdialysis. MEAs report current variations shaped by several variables including proper preparation and prior calibration for successful use. The measurement of interferents and metabolites can potentially be overcome by surface modification of MEA as well as by using self-referencing techniques. Future technological improvements in the design and fabrication of implantable electrodes are needed to resolve these limitations.

8. Moving into the Future: Recordings in Freely-Moving Animals

In vivo electrochemical recordings using amperometry in awake, freely moving animals allow for assessment of real-time neurotransmitter changes during behavioral tasks. This remained challenging due to the depth of the brain regions and the necessity to record from freely behaving animals, but advances in microelectrode fabrication allow for probing chemical events for longer-term experiments. Several studies have begun to use this approach to study spontaneous neurochemical events in relation to well-defined, quantifiable behaviors of feeding, reward-seeking, sleep-wake, addictive and attention-deficit hyperactivity behaviors [191–195]. Continuing to study the dynamic neurotransmitter changes and behaviors in other disease models including TBI would benefit greatly to our understanding of post-traumatic neuronal signaling. These recordings can also be synched to video recordings of behavior, linking behavior to amperometric recordings. Direct assessment of neurotransmission provides for simultaneous measurement with other measurements of neuronal activity with millisecond precision. Emerging approaches involve the design of microelectrodes capable of concurrent assessment of neural electrical activity with local field potentials (LFPs) [196,197]. The integration of neurochemical information with electrophysiological approaches will greatly expand our understanding of the circuit-neurotransmitter relationship. Moreover, the integrative approach has been validated by several studies [198] providing key insight into both normal neural circuit dynamics and its dysregulation in disease [199].

Advances in in vivo assessments have enabled us to gain insight into the nature of the subthreshold events that underlie evoked action potential discharge in anesthetized and awake animals. Specifically, direct measurement of brain chemical signaling provides valuable information when combined with other physiological methods to manipulate neuronal activity with sophisticated observational work and casual manipulation studies. Targeting neuronal systems infers causality between neurotransmitter events and behavior in conjunction with optogenetic-based [197] or chemogenetic (DREADD) approaches [200]. Optogenetics combined with in vivo electrochemical assessments has already proven to be effective in studying glutamate signaling in both hippocampus and frontal cortex in anesthetized animals [197,201]. This is particularly important for the study of circuit-level mechanisms of disease in vivo, when applied to existing behavioral models as output measures can provide insights for future clinical translation. Changes in metabolic and vascular response occurs as a consequence of neuronal activity to restore brain homeostasis, altering tissue oxygenation. Such changes form the basis of neuroimaging methods such as functional magnetic resonance imaging. Metabolic brain disorders alter oxygen utilization and tissue oxygen tension (pO_2) thereby disrupting neuronal circuits [202,203]. While non-invasive neuroimaging methods provides for a great clinical advantage, the responses observed are influenced from several other factors including hemodynamic response and limited spatial resolution [204]. The ceramic-based platinum MEAs have been used for in vivo recording of changes in pO_2 in anesthetized rat brain with excellent electrocatalytic activity towards oxygen reduction and low detection limits [177]. In a proof-of-concept experiment, our lab recently demonstrated robust reduced oxygen consumption and decreased LFPs in the whisker barrel circuit after mFPI at 1 day post-injury [205], implicating alternative approaches for monitoring changes in behaviorally relevant circuit function after TBI.

Exceptional progress had been made towards electrochemical analysis of behaviorally relevant neurotransmitter signaling in the extracellular space as demonstrated by recordings in non-human

primates [206,207] and swine [208]. In 2013, a new wireless sensing device coupled with voltammetric detection for electrochemical monitoring was demonstrated in a late-stage PD [209]. An emphasis has been made towards further miniaturizing biosensors to record at the level of the synapse, increasing temporal resolution for more accurate changes in release/reuptake, improving selectivity (distinguish neurotransmitters) and signal-to-noise, and increasing the number of targets that can be simultaneously recorded. Several strategies have also been developed to minimize tissue damage during insertion, biocompatibility, attenuate foreign body response following implantation, increase longevity, improve performance and resolution, reduce tethering artifact (i.e., wireless), and increase electrode flexibility by multiple groups. However, these approaches have yet to be combined into a single MEA [210]. While limitations to clinical applications still exist, the evolution of this technology is rapidly moving toward a point where the benefit of implantation and the information gained from recordings will outweigh the risk to the patient.

9. Peripheral Influences on Neurotransmission and PCSs

Throughout this review, we have focused on circuit reorganization and dysfunction as primary mechanisms towards changes in neurotransmitter signaling after TBI. The following section is intended to acknowledge peripheral influences that have recently been indicated in mediating neurotransmission that may be relevant to treatment and application for in vivo neurotransmitter monitoring.

9.1. Neuroendocrine and Neuroimmune Interactions

Emerging studies have reported that a substantial population of TBI patients, as high as 25%, report chronic endocrine dysregulation involving growth hormone, gonadal, thyroid, adrenal and antidiuretic hormones [211–213]. Hormone receptors are located on neurons and can influence circuit function. Yet, few studies address the impact of neuroendocrine dysregulation on neurochemical signaling related to TBI-induced PCSs exists. For example, after experimental TBI, chronic dysregulation of the HPA-axis has been implicated by changes in baseline circulating glucocorticoid levels and in response to stress in a sex-specific manner [214–216]. Glucocorticoid receptors are located on every cell type and modulate neurotransmission and neuroinflammatory response [217]. With the growing recognition of neuroendocrine–immune interactions, the potential microglial contributions to endocrine dysregulation have been proposed based on the reactivity state of the microglia [218]. The enhanced neuroinflammatory response stemming from immune-mediated central glia, particularly the microglial response might set the stage for depressive-like features [219].

9.2. Sex Hormones

Sex-related differences in human brain structure and susceptibility to neuropsychiatric diseases have been documented [220]. Yet, again, their role in the persistence and development of PCSs have not been fully explored. Reports indicate sex differences in many neurotransmitters including serotonergic, cholinergic and adrenergic systems [221–223]. Findings also suggest that sex hormones, including estrogen and progesterone, mediate worse outcomes among women of childbearing age after TBI [224]. Ovarian hormones are known to exhibit modulatory role on synaptic transmission regulating presynaptic neurotransmitter release or postsynaptic receptor action as a possible target for their influence after TBI [225,226].

9.3. Gut–Brain Axis

There has been a growing support of the influence of multiorgan responses on the acute and chronic effects of TBI. Such interactions between the brain and the systemic physiology involving the function of body organs after TBI can indirectly influence neurotransmitter systems or modulators. The sequela of TBI induces significant alterations in metabolic and enteric function, affecting peripheral systems. TBI survivors often report of gastrointestinal dysfunction with reports increased gut permeability [227], reduced gastric emptying [228] and intestinal contractility [229]. Two communication routes for the

gut–brain axis are through the vagus nerve and the gut microbiota [230]. Vagus nerve stimulation is currently being evaluated preclinically and clinically for improvement in motor, cognition, edema, inflammation, and BBB breakdown [231]. Gastrointestinal disorders consequently disrupt the microbiota (gut bacteria) and accumulating data suggesting that the microbiome is the key regulator of the bidirectional gut–brain axis to influence brain function, behavior and host physiology [232]. Preclinical reports have shown microbiota dysbiosis after TBI [233,234]. Yet the link to PCSs has not studied. Evidence points to behaviors linked to neurotransmission that are influenced by microbiota [235] with certain bacteria possessing the capacity to generate neurotransmitters and/or precursors to neurotransmitters. It has been found that several bacteria including *Bifidobacterium* and *Lactobacillus* spp. produce GABA, *Bacillus* spp. produce DA, *Lactobacillus* spp. produce ACh and *Escherichia* spp. produce 5-HT [236–239] while their implications on brain function are slowly being unraveled. Particularly, the gut microbiome is known to regulate tryptophan metabolism necessary for the synthesis of 5-HT in the brain [240]. The intestine can also serve to be an endocrine organ through the production of microbial neurometabolites. Specifically, GABA is produced directly or indirectly by certain commensal microbes to influence gut–brain interactions [241].

9.4. Other Organs

Mild TBI enhances liver inflammatory markers by altering the redox homeostasis and given their wide implications for their interaction between brain and body, leakage of pro-inflammatory factors through the disrupted BBB can exacerbate brain injury pathology [242–244]. TBI can promote cardiovascular risk factors through increase in expression of pro-inflammatory chemokines and apoptosis [245,246]. The spleen is an important lymphoid organ innervated by sympathetic nerve fibers that are in contact with splenic immune cells to create a neuroimmune link [247]. Enhanced pro-inflammatory levels have been characterized as an acute response to diffuse TBI [248]. The neurotransmitters of the sympathetic nervous system bind to receptors on the surface of immune cells and within the microenvironmental niche of the spleen, immune cell receptors bind neurotransmitters to exert effects on nerve terminals [249].

10. Concluding Remarks

In this review, we have discussed the clinical and experimental evidence on the acute and chronic pathophysiological responses after mild TBI, animal models of diffuse brain injury, alterations of neurotransmitter systems that underlie the circuit deficits which can compromise and/or compensate the processes that enables neuronal response to injury. Alterations in the TBI-induced neurotransmitter systems that form the core machinery expressed by most of the neurons have been considered crucial in the development of PCSs. Multiple in vivo electrochemical measurements with increasing resolution offers a portal to directly quantify and characterize the dynamic real-time neurotransmitter signaling mechanisms that operate during behavior to provide important details of the pathophysiology of circuit function. Advances in the application of interference tools permit more direct modulation of in vivo control of neurotransmitter signaling in animals engaged in freely moving and defined behaviors (see Figure 1 for details). Given the unmet clinical need to modulate neurochemical signaling in the diseased state, including TBI, the future of electrochemical characterization can be fully adapted to apply behavioral shaping pharmacological interventions that normalize neurotransmitter signaling.

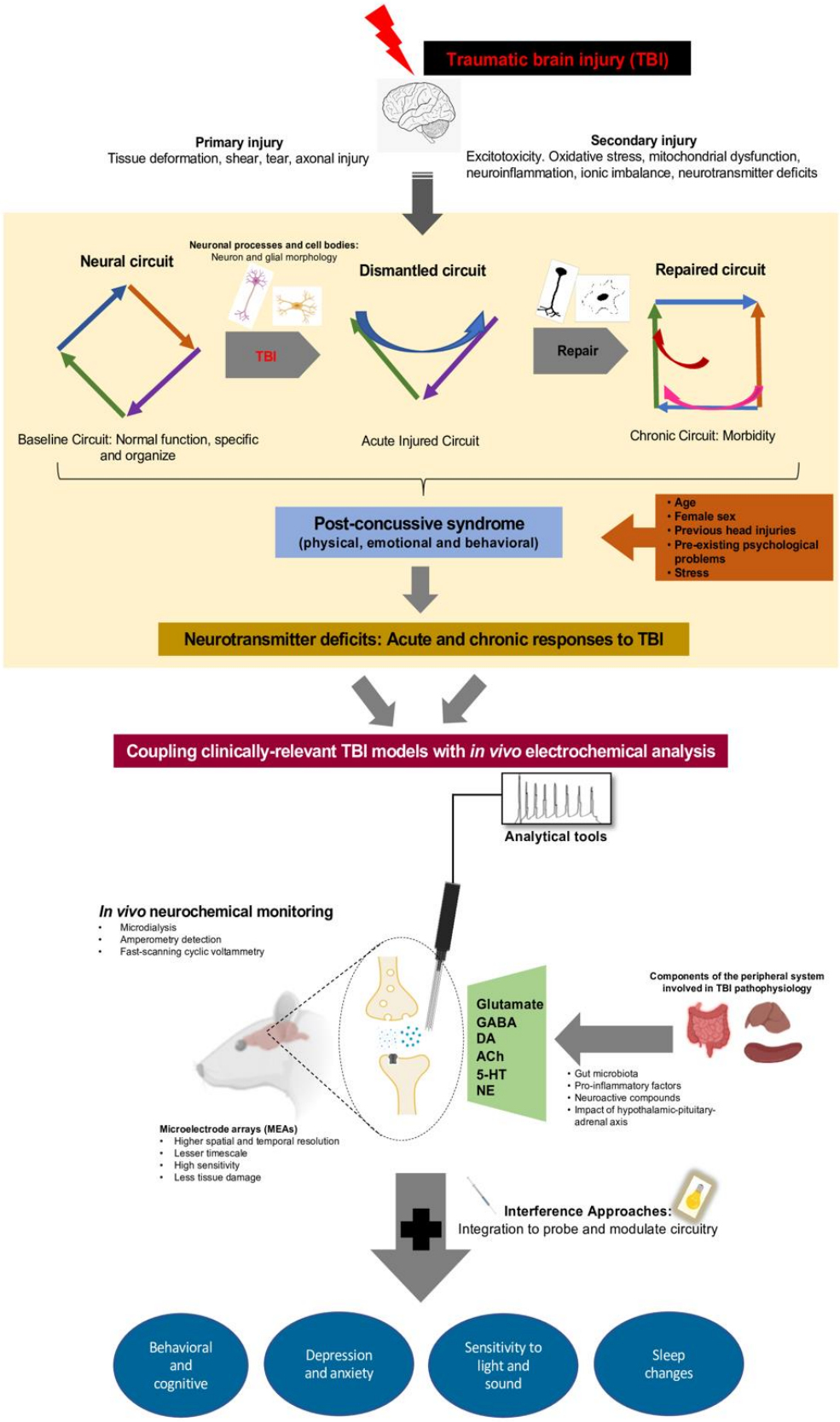

Figure 1. Cartoon summary highlighting the approaches to monitor circuit disruption and behavioral manifestations after traumatic brain injury (TBI). Mild TBI initially manifests as primary and secondary

injuries leading to acute and chronic neurological deficits, contributing to morbidity of injury. The repair and reconnection of broken circuitry that follows TBI leads to formation of maladaptive circuitry. The characteristic pattern following injury provides potential context for pathologies of neuronal processes and cell bodies subsequent to injury-related deficits in metabolism or neuronal function. TBI-induced damage to neural responses evolve into diffuse circuit disruption leading to development of post-concussive symptoms (PCSs). Neurotransmitter systems are important components of the neuronal circuitry (also influenced by components of peripheral system) that modulate many of the behavioral functions that are impaired following TBI. The assessments of these neurotransmitter changes can capture important aspects of brain-injured circuitry and offers a potential target for modulation. Experimental studies involving use of different methods for recording extracellular neurotransmitter levels provides for evaluating changes in neurotransmitter signaling, where measurements are made with high spatial and temporal resolution. Coupling clinically-relevant TBI models that show chronic behavioral deficits with in vivo technologies capable of real-time monitoring of neurotransmitters in behaviorally relevant circuitry provides a powerful and innovative approach to understanding compensatory changes in neurotransmitter signaling as a TBI consequence. In experimental models, the use of interference tools permits more direct modulation of in vivo control of neurotransmitter signaling in animals engaged in freely moving and defined behaviors. This approach can be used to understand the impact of pharmacological interventions on both therapeutic regulation of TBI altered neurotransmission capable of mitigating behavior.

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