Diffuse traumatic brain injury and the sensory brain

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Summary

1. In this review, we discuss the consequences to the brain's cortex, specifically to the sensory cortex, of traumatic brain injury.

2. The thesis underlying this approach is that long-term deficits in cognition seen after brain damage in humans are likely underpinned by an impaired cortical processing of the sensory information needed to drive cognition or to be used by cognitive processes to produce a response.

3. We take it here that the impairment to sensory processing does not arise from damage to peripheral sensory systems but from disordered brain processing of sensory input.

The epidemiology and clinical consequences of traumatic brain injury

Traumatic brain injury (TBI) can result from any blow to the head such as in car accidents, sporting field blows, physical abuse, falls, military conflict and terrorist activity.[1-3] The first four account for most TBI in civilians and the latter two for a very large recent increase in TBI among defense personnel and civilians.[1-3] Globally, adolescents from 15-19 years, and adults > 65 years constitute groups likely to sustain a TBI;[1] in Australia and New Zealand TBI is more commonly encountered in young males than females and is primarily caused by automotive accidents from speeding.[3]

Mortality rate for severe TBI is 20-30% in developed countries and as high as 90% in developing countries.[4] While the death rate has declined over the past 20 years, the morbidity rate has remained invariant despite advances in critical care and diagnostic techniques; hospitalization in Australia has increased by 7%-33% (depending on TBI type) from 1999/00 – 2004/05.[2] Although some drugs and physiological techniques have shown therapeutic potential in experimental models, phase I-III clinical trials have proven ineffective or even harmful to patients.[2]

In general terms, TBI is classified as focal or diffuse, although both often co-exist. Focal injury describes direct physical damage to the brain, resulting from a direct blow to the head,[5,6] and is often characterized by lesion formation, haematomas and haemorrhages detectable using imaging techniques such as computer tomography (CT) and magnetic resonance imaging (MRI).[7] The majority of people suffering TBI have diffuse TBI,[1-3] which is caused by inertial forces induced during rapid acceleration/deceleration of the head,[8] and is highly prevalent in cases of closed head injuries (such as those caused by falls, accidents, child abuse). Even with sophisticated imaging techniques,[9] it shows little visualizable damage other than axonal damage.[10] Mild diffuse injury is known to cause cognitive deficits and memory loss,[11] which are suggested to be due to neuronal damage.[12] Early treatment for injured neurons is currently unavailable in clinical settings.[7]

Generally, diffuse injury-induced brain changes are believed to involve subtle alterations in neuronal function and circuit dynamics. Because of this, it is held to be under-diagnosed and likely to affect up to 600 people per 100,000 people annually.[2] TBI outcomes can range from physical disability to memory loss and cognitive dysfunction including very severe and life-long debilitating deficits in cognitive and sensorimotor function.[13,14] Cognitive deficits include attention and memory deficits, reduction in information processing speed,[14] and psychiatric disorders.[5] Motor impairments include deficits in fine motor skills such as finger-tapping and grip strength,[15] and coordination, where patients were found to have impaired gait and balance.[16] Persistent sensory deficits have been extensively demonstrated across a number of tasks[17,18] and across modalities.[19,20] People with mild to moderate diffuse TBI usually recover motor skills fully, but cognitive deficits and memory loss tend to be persistent.[7,14]

Phases of brain injury

TBI occurs in two phases.[1-3,5-8] Primary injury occurs at the time of trauma and can be either from direct physical impact (focal TBI), or from inertial forces due to rapid acceleration-deceleration of the brain (diffuse TBI). This is aggravated by hypoxia from lung blast injury or brain stem damage, which occurs in almost 40% of TBI patients. TBI and can cause loss of neuronal cells in the immediate vicinity of the trauma. Primary injury is then followed by secondary injury processes which are responsible for the prolonged activation of many molecular cascades as a part of normal pathophysiological responses and cause delayed secondary brain damage to the already damaged brain tissue, through multi-factorial processes that include oxidative stress, excitotoxicity, hypoxia-ischemia, inflammation and cerebral oedema.[3] These secondary brain injury processes exacerbate the primary damage or evoke new damage, affecting neuronal survival and function in human and animal models of TBI. They are often the most destructive component of TBI and responsible for most of the neurologic deficits observed after TBI in both human studies and experimental models of TBI.[5,7,21]

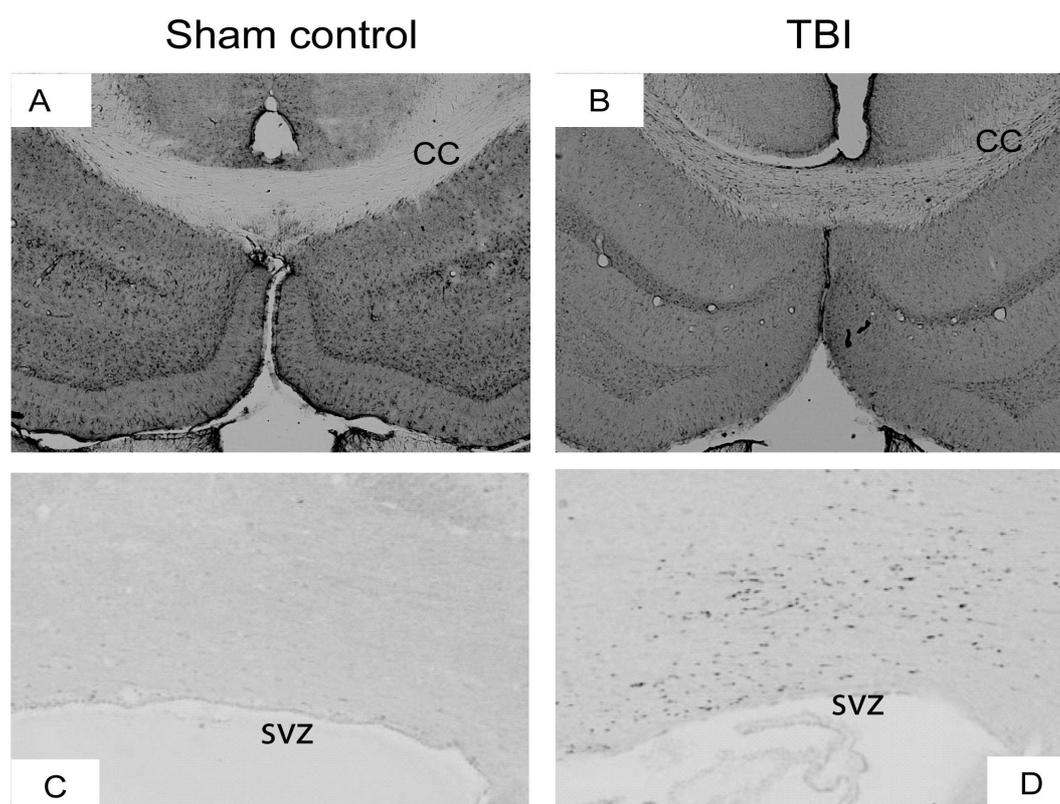In addition to the pathologic outcomes of primary and secondary brain injuries, human TBI is often coupled

Sham control

TBI

Figure 1. Morphological indices of diffuse axonal injury in the impact acceleration model. *All panels show coronal sections of the brain at 1.3 mm caudal to bregma.* **A&C** *are data from a sham surgery control animal,* **B&D** *from a diffuse traumatic brain injury animal.* **A&B** *show the region of the corpus callosum (CC) to show the immunohistochemical staining for GFAP as an index of astrocytosis. Note the absence of any astrocytosis in the control animal and the "streaking" staining throughout the CC in the TBI animal.* **C&D** *show the region of the sub-ventricular zone (SVZ) in the same brain region to show the immunohistochemical staining for neurofilament-heavy chain (200 kDa) as an index of axonal injury. NF-H is one of three NF proteins that make up the axonal cytoskeleton with "sidearm" domains which can be phosphorylated following injury that may then contribute in some degree to enlargement of the axonal diameters and can impair axonal transport following TBI. NF-H and β-amyloid precursor protein are standard markers of TBI. Note the absence of any staining in the control animal and the staining in the TBI animal.*

with post-traumatic hypoxia[22] from respiratory depression, lung puncture, tracheal obstruction, and cerebral hypoperfusion.[23] Post-TBI hypoxia exacerbates neurological deficits.[24] It is known that axonal injury and hypoxia-ischemia on their own increase oxidative stress and cause brain tissue damage.[25] It is likely that axonal injury will cause sensorimotor and cognitive deficits resulting from impaired synaptic function; and post-TBI hypoxia will exacerbate sensorimotor, cognitive and memory dysfunction when compared with TBI alone.

Factors disrupting neuronal function in TBI

Axotomy

Diffuse TBI does not typically cause overt lesions or cell death in cortex or thalamus but causes widespread damage to neurons and cerebral vasculature.[12,26,27] In particular, white matter tracts of corpus callosum and brainstem suffer axonal swelling and injury (see Figure 1);[28] and axonal injury is the main feature of diffuse brain damage and is responsible for the severe disability seen in patients with TBI.[29] Axotomy occurs at the time of injury and continues during the secondary injury phase. Rapid acceleration/deceleration induces shearing forces on the axons which cause stretching and tearing damage.[30] Disruption and severing of the cytoskeletal structure of the axon results in compromised axonal protein transport and intracellular protein accumulation at the point of axonal breakage to form retraction bulbs[31] as early as 1 hour post-trauma.[32] As a part of secondary axonal damage, increased membrane permeability occurs within 6 hours of TBI,[33] resulting in cellular oedema. Trauma-induced excessive Ca^{2+} influx into the cell impairs normal cellular metabolism, causes mitochondrial swelling[34] and disrupts the axonal cytoskeleton.[31] Neurofilament disruption (Figure 1D) can also occur through protein phosphorylation and side-arm proteolysis.[35] All these mechanisms result in secondary axotomy, thought to occur hours to days after the initial damage.[8] Beta amyloid precursor protein (β-APP)

accumulates at the point of axonal severance, indicating impaired axonal transport post-TBI.[36]

Diffuse axonal injury results in increased astrocytosis and macrophage infiltration up to 2 weeks post-injury,[25] mainly due to cytoskeletal breakdown during primary and secondary injury. While cell death in cortex is not generally seen after diffuse axonal injury[12] these neurons undergo atrophy, with increased neuronal degeneration in the upper cortical layers 48 hours post-injury.[27,37] In rodent sensory barrel cortex, the atrophy spreads from upper and input layers at day 1 post-injury to middle and deep layers by day 7, and to deep layers, white matter and inter-barrel septa by day 28.[12] Diffuse injury causes axotomy and neuroinflammation in the thalamus (VPM), again with no neuronal loss.[38]

Oxidative stress

In hypoxia-ischemia, which can occur after TBI, impaired mitochondrial function leads to incomplete reduction of O_2 and the formation of reactive oxygen species (ROS) such as the free radicals, the superoxide anion (O_2^-), and the hydroxyl radical (OH), and hydrogen peroxide (H_2O_2), and reactive nitrogen species (RNS) such as peroxynitrite ($ONOO^-$).[39] Normally, ROS and RNS are scavenged and detoxified by the endogenous antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase. Excessive free radical production overwhelms endogenous antioxidative mechanisms resulting in oxidative damage[39] by reacting with lipids and proteins and altering their structure and function. For example lipid peroxidation by free radicals leads to a loss of membrane integrity and function. In addition to increased ROS formation during hypoxia, mechanically stretched neurons also increase ROS and RNS formation as a result of increased intracellular [Ca^{2+}], making them prone to oxidative stress.[40] Neurons are particularly susceptible to oxidative damage due to their high oxygen consumption and the high lipid content of the myelin sheath, and low levels of antioxidant activity.[41] Neuronal cell death, through apoptosis and necrosis, is induced by oxidative stress.[39,41] This occurs through membrane disruption and DNA damage, which disrupts mitochondrial function and further propagates oxidative stress.[40] A strong correlation exists between the extent of oxidative stress and the pathogenesis of TBI,[42] Increased levels of oxidative stress markers are found in human cerebrospinal fluid after TBI,[43] and free radicals play a known role in mediating cytoskeletal damage and axonal transport following diffuse TBI.[44]

Disruption of neuronal functions and interactions due to synaptic and ionic imbalances

High concentrations of glutamate are released during TBI, likely due to stretch/chemical stimulation of pre-synaptic terminals,[45] leading to excitotoxicity of post-synaptic neurons. Up-regulation of glutamate release regulators such as complexin I and II at the terminal also contributes to increased glutamate release.[46] In hypoxia-ischemia, uptake by adjacent astrocytes of excessive glutamate in the synaptic cleft is impaired.[47] Extracellular glutamate accumulation can also occur following an increase in blood-brain barrier permeability after trauma.[48] The accumulation of excessive glutamate and other excitatory amino acids in the synaptic cleft results in activation of postsynaptic NMDA and AMPA receptors, enabling excessive Ca^{2+} influx into the post-synaptic neuron.[49] High intracellular Ca^{2+} increases mitochondrial damage leading to a disruption of intracellular metabolism and to production of free radicals by activating enzymes such as phospholipases and proteases.[50-52]

Excessive glutamate release and decreased removal after injury leads to prolonged glutamatergic depolarisation which likely extends the open time of voltage-gated Na^+ channels.[53] Influx of Na^+ is followed by Cl^- ions, which results in higher intracellular osmolality. Water enters the cell down the concentration gradient and results in cellular swelling and cytotoxic oedema.[49] The excitotoxic release of free radicals can further potentiate glutamate toxicity by inhibiting astrocytic glutamate uptake.[54]

The TBI-induced changes in glutamate release and the consequences for ionic balances and neuronal function have been well studied in the hippocampus, in the context of the memory impairment seen commonly in human TBI and in animal models of TBI.[13] Following TBI, there is increased excitability of pyramidal neurons of the CA1 region of the hippocampus,[55] resulting from increases in extracellular K^+ and glutamate concentrations, and intracellular [Ca^{2+}].[56] Cerebral ischemia induces an increase in extracellular [K^+] and intracellular [Ca^{2+}] during depolarization.[57] Pyramidal hyperexcitability could lead to deficits in memory formation and processing, and is also linked to post-TBI development of seizure activity, for which the hippocampus is a known epileptic focus.[58] It has been proposed that TBI-induced change in ionic balance between intra and extracellular environments is responsible for alterations in the synaptic phenomenon of long term potentiation (LTP) that is believed to underlie some forms of memory.[59,60] The changes in ionic balances could be exacerbated by oxidative stress since free radicals can disrupt ionic balance in neurons by compromising membrane function[61] and impairing ion pump/channel activity.[62] Dysfunctional channels and pumps could lower the threshold for action potentials and make hippocampal cells more prone to hyperactivity.[63]

However, in contrast to these observations indicating hippocampal hyperactivity from transmitter and ionic disruptions, other TBI studies have shown that TBI causes a suppression of CA1 neuronal activity and an inhibition of LTP.[64-66] These changes in TBI are consistent with changes in inhibition, and the increase in excitation in the dentate gyrus (DG) could be a result of direct increases in excitation or impaired inhibition that would normally suppress excessive excitation.[64] Similarly, a decrease in excitatory CA1 activity could be due to a direct or indirect increase in inhibition.

Changes in inhibitory activity are likely not the only explanation for the region-specific differences in the hippocampus. Enhancing and blocking inhibitory action in
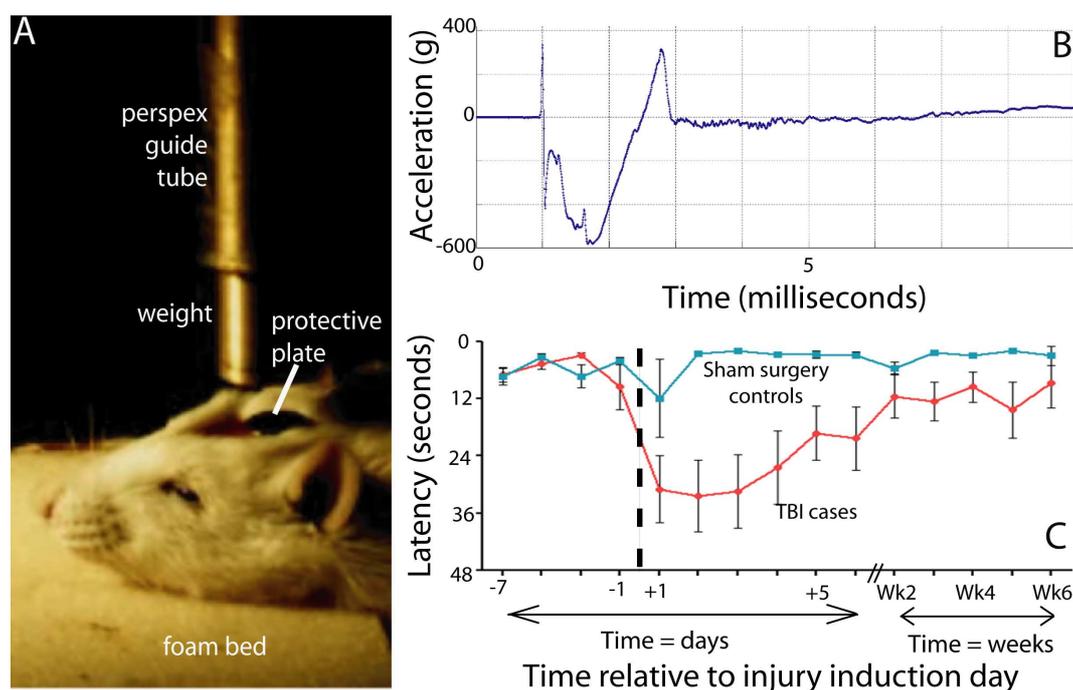
Figure 2. The impact acceleration method for induction of diffuse traumatic brain injury and behaviour outcomes from the process. *A shows the components of the impact injury model (see Marmarou et al., 1994[26]). B shows the profile of the acceleration of the head in this injury process. C shows the long-term sensorimotor deficits induced by this injury; data illustrated show the time taken for the rat to remove an adhesive tape stuck to the forepaw. The bold vertical dashed line represents the day on which TBI was induced – no behaviour tests were conducted on that day. Data represent mean ± SEM. Sham surgery controls, n = 14; TBI, n = 19.*

the DG and CA1 area respectively, after TBI has shown that these treatments were only able to partially restore fEPSP slopes in both regions, suggesting that other factors governing regional changes in excitability are involved.[64] Another factor that could contribute to the lack of excitation in the CA1 region might be the loss of excitatory or inhibitory neurons due to both primary injury and secondary injury mechanisms.[67]

Neuroinflammation

Secondary brain injury involves neuroinflammation due to activation of an immune response of cytokine production, microglial activation and macrophage infiltration (see Figure 1B).[68] Activation of inflammatory cascades is a normal cellular response following injury, functioning primarily to protect and repair the damage caused by the initial injury. However, the toxic mediators released at the early stages of inflammation cause further injury to the already damaged brain.[68] An inflammatory response involves production of pro-inflammatory cytokines like interleukin-1 (IL-1), IL-6 and tumour necrosis factor (TNF-α), and anti-inflammatory cytokines such as IL-10 and IL-12, all of which are seen in the cerebrospinal fluid of TBI patients within a few hours of the primary injury.[68] Inflammatory cytokines IL-1α, IL-1β and IL-18 are also increased after TBI.[69] The detrimental properties of these pro-inflammatory cytokines have been

demonstrated in studies that use IL-1β and TNF-α receptor antagonists to decrease neuroinflammation and cell loss after injury.[70]

Concussive closed head impact models the damage seen in car and sporting accidents

Many experimental models have been developed to mimic human TBI each causing specific kinds of damage and thereby modelling different forms of head trauma in humans (*e.g.* concussion injury, whiplash trauma or acceleration/deceleration forces). The three most well-established models are the fluid percussion (FP),[71] closed cortical impact (CCI),[72] and weight-drop impact/acceleration (WDIA) models.[73] Both the FP and CCI models result in a combination of focal and diffuse injury, and produce similar pathologies including cerebral vascular damage, oedema and axonal injury.[73,74] Our model of choice is the WDIA model (Figure 2) developed by Marmarou *et al.*[26] to investigate only diffuse injury.[27] We have examined this model with high-speed videography (Figure 2A) and identified three major processes contributing to, or causing damage in this model: (a) object impact onto the skull creating a shock wave like phenomenon that is transmitted into the brain, (b) relative movement between skull and brain, and (c) whiplash motion of the neck. These effects are likely to be very similar to what occurs in motor vehicle accidents, as well as

likely in sporting field accidents. We believe that each of these contributes mainly, if not solely, to one facet of the traumatic brain injury seen with the Marmarou *et al.* model.[26] The impact force (Figure 2B) is likely to cause rapid suppression of neuronal activity in brains areas directly impacted by the blow and this can have flow-on effects to more distant brain areas which receive input from the immediately-affected regions. It is likely that the second factor contributes mainly to the diffuse traumatic axonal injury that is characteristic of this model. Finally, the last factor is likely to cause rupture of the brainstem blood vessels, resulting in disturbances to respiratory and cardiac control regions in the brainstem, and can lead to death through respiratory and/or cardiac failure.

In any case, this model replicates the pathology of diffuse injury of wide-spread traumatic axonal injury without focal lesions, and causes long-term sensorimotor and cognitive deficits (Figure 2C), comparable to human diffuse brain injury. We have applied this model to the study of how traumatic brain injury affects sensory encoding in cortex.

Sensory deficits may underlie behaviour changes in TBI

The causes of the prolonged functional deficits in diffuse TBI are rarely known.[1,2,5] The absence of obvious cell death and the array of cognitive and memory deficits[1-3,13-20,70-72] suggests a substantial but subtle *functional* alteration with ramifying consequences, and one beyond resolution of standard imaging/histology. It is worth noting here that TBI-induced deficits in cognition, memory and movement are invariably viewed as resulting from damage to brain areas specific to those functions. However, most TBI sufferers show changes in how they process sensory information and since sensory input and it's processing by the sensorium are critical to understand the world and guide complex behaviours; sensory processing deficits may easily affect these behaviours. It has been recognized that at least some impairments may involve disruption of the integration of sensory input.[1]

Sensory systems have many advantages for examination of functional alterations in diffuse TBI. Sensory input can be very precisely specified and directly related to everyday objects and experiences, and sensory receptor surfaces are generally mapped very precisely and topographically to at least the primary sensory cortex. This cortex is laminated in a very highly organized fashion with inter-laminar interconnections often well described, and the neuronal computations occurring within the functional unit of a sensory cortex (the column of cells in the grey matter stretching from cortical surface to the white matter and spanning cells across the laminae) are accessible to study in a manner that links these computations well to behaviour. These attributes of sensory input and of the sensorium makes sensory cortex an ideal test bed for examining the hypothesis that alterations in functional interactions in cortical circuitry underlie the deficits of diffuse TBI. We first briefly describe the sensory deficits that occur in diffuse TBI, before expanding on the sensory cortical

changes in a unique experimental model that allows interpretation of electrophysiology in parallel with extensive on-going work on the cellular and molecular changes in the appropriate cortex.

In humans, persistent sensory deficits related to diffuse brain injury occur across modalities.[19,20,75-77] Galvin and colleagues[76] reported changes such as enhanced sensitivity in visual, auditory and touch processing in paediatric TBI patients (as reported by an assessment scale provided to care-givers) for a year after injury. Many studies report hypersensitivity to sensory stimuli.[75,77] Patients with TBI often show changes specific to processing of complex sensory cues,[18] *e.g.* Brosseau-Lechaine *et al.*[17] showed increases in dynamic orientation-identification thresholds up to 12 weeks post-injury, while more simple static thresholds remained unaffected. Other studies using more direct measurements of sensory abilities have reported cases of auditory and visual changes in adult TBI, in the form of longer P300 latencies and smaller amplitudes.[19,20] Speeded motor tasks and response time tasks are also affected in mild/moderate diffuse TBI,[7,16] again suggesting disturbances in sensori-motor processing; and there are many long-lasting cognitive impairments even after motor function has recovered *e.g.* Faul *et al.*, 2010,[1] Brosseau-Lachaine *et al.*, 2008.[17] It still remains an open question as to the extent to which the long term sensory deficits may contribute to the cognitive and motor deficits.

In rats, our experimental species, mild-to-severe TBI causes long-term motor deficits in standard behaviour tests such as rotarod and beam walk tasks up to 6-8 weeks post-TBI.[78] Sensory processing deficits have been seen using tasks dependent on sensory input solely from the large face whiskers (a critical sensory system, as detailed in the next section below) even over 6 weeks post-injury.[12,78] These sensorimotor deficits could be due to peripheral changes or disruptions in sensorimotor processing networks.[37] Whisker-based sensory behavioural morbidity has been attributed to thalamic neuronal damage and atrophy.[12,37] Thalamic inputs show some regrowth at one-month post-axotomy from re-establishment of trophic support, as indicated by expression of axonal and synaptic markers such as GAP-43 and synaptophysin in thalamus and hippocampus early after TBI[37,79] and in retina after retinal axonal injury.[80] Persistence of behavioural morbidities over 6 weeks post-injury in our study[78] suggests axonal repair over this time does not compensate for TBI-induced circuit changes or may even be maladaptive.

The rat barrel cortex is an appropriate model for studying sensory cortex changes in TBI

In rats, the large face whiskers and olfaction provide the major sensory inputs for interfacing with the world and the whisker system provides the same high-fidelity information as human vision, hearing and touch.[81-87] The rat mystacial pad system is highly organized, with short (microvibrissae) and long (macrovibrissae) whiskers arranged in a rostral to caudal fashion, respectively, along the snout with the whiskers arranged in a grid-like pattern

of arcs and rows.[108] Rats gain vibrissa information through active "whisking" under muscle control over objects or from passive deflections from head motion or objects moving past.[105-103] In human touch, too, discrimination of gratings by active hand movement is the same as when the grating is moved passively over the hand and both auditory and visual discrimination are equally good with head/eye movement as without such movement.

This sensory system offers great advantages for directly linking sensory encoding to behaviour because natural whisking patterns are well described for many behaviours.[88-98] The whisker system's information-bearing parameters have strong parallels with those in human touch and translate to human touch for discriminating fine-textured objects.[99] Two other factors also play an important role in making this system attractive for studying sensory cortex in TBI. Whiskers form a constant pattern on the face and are easily manipulated to apply a range of simple and complex stimuli. Finally, the types of mechanoreceptor endings of primary afferent neurons in the whisker follicle and the neural pathways through brainstem and contralateral thalamus to the input layer (Layer IV) of the postero-medial barrel sub-field (PMBSF) or *barrel* cortex of primary somatosensory cortex are well described. Barrel cortex neuronal physiology, especially in layers II-IV (mainly lemniscal input), to simple whisker deflections is well detailed.[100-114]

The extensive use of rats to study anatomical and molecular changes in TBI, coupled with the great depth of knowledge on the use of whiskers in extraction of information about the world, provide powerful reasons for use of the rat macrovibrissal system and the associated barrel cortex[115] to study sensory cortical changes in TBI. A limited number of studies have done so[37,116-118] and it is known that diffuse TBI results in prolonged heightened sensory sensitivity to whisker stimulation in behaving rats,[116] correlating with heightened cFos activation in barrel cortex 6 weeks post-injury[37] following on from reduced cFos activation in the first week post-injury. Interestingly, these changes were not associated with detectable cell loss in barrel cortex.[12] The absence of detectable damage at these gross levels has led to a shift in emphasis in the rat macrovibrissae system to thalamic changes[38] as the basis of TBI-induced deficits in sensory neuronal function.

Changes in sensory cortex excitability with diffuse TBI

Some recent studies have started to hint at the nature of the electrophysiological changes in sensory cortex caused by TBI. Immediately following brain injury, there is a global suppression of sensory cortical responses in Layer 4 between 5 to 20 minutes after injury, followed by a period of increased activation (above baseline activity) at approximately 2 hours after injury.[117] This was also seen histologically by Hall & Lifshitz[37] who found that over 6 weeks, there was an initial attenuation in cFos stained neuronal activation of the primary somatosensory cortex lasting for one week post-injury, followed by an increase in activity in the cortex, thalamus and hippocampus above

sham levels. The mechanisms behind long-term hyperexcitability post-TBI have been studied electrophysiologically in hippocampus[119,120] and cortex through histological techniques and the study of field potentials.[37,118] Hyper-excitability in these studies has been linked to increases in excitatory potentials as well as decreases in inhibitory efficacy, supporting the theory of imbalanced excitation/inhibition.[64,65,119]

However this has yet to be tested directly. Only a very sparse number of studies have investigated electrophysiological changes in sensory cortex after injury, and none have studied long-term alterations in cortical activation. Three days after brain injury, evoked potentials from somatosensory cortex have significantly longer latencies and reduced field potential slopes, extracted through averaging the individual depths at which the maximal field potential was found for each animal,[118] in keeping with decreased metabolic activation as early as 4 hours, and up to 24h after injury.[121] Post-TBI hyperexcitability after cortical isolation injury has been linked to increases in frequency and amplitude of spontaneous excitatory synaptic currents and a decrease in frequency of spontaneous inhibitory synaptic currents in Layer 5 at 2-6 weeks post-injury though not in supragranular layers.[122]

Recently we have examined the changes in barrel cortex immediately after, and long after, traumatic brain injury created using the impact acceleration method.[26] Our studies suggest that three previously described factors play a significant role in the immediate damage caused by this method: (1) an impact stress wave travelling through the brain; (2) a relative motion between skull and brain; and (3) a whiplash motion of the neck affecting brainstem neural and vascular structures. Our electrophysiological data suggest that the immediate post-TBI changes in cortex are dominated by the stress wave phenomenon causing a suppression of activity through the cortical laminae in a distance-dependent manner: changes in population responses are greatest in the supra-granular layers and smallest in the infragranular layers (Figure 3).[123] The firing rate changes were not accompanied by changes in response timing as might be expected for relayed sub-cortical effects. This is consistent with the fact that the firing rate changes occurred as a result of cortex-specific mechanisms.

We have also examined the long-term effects of TBI[78] 8-10 weeks after TBI created using the same impact acceleration method. Some effects were similar to those seen immediately after impact injury and other effects suggested a process of recovery over that time period (see Figure 4; compare top row of panels against bottom row of panels). As in the short-term case, supra-granular hyper-excitation is again seen in the larger cells and is unaccompanied by any changes in response timing, again consistent with our conclusion of cortex-specific changes in TBI. Again, there was no hyper-excitation in input and infra-granular layers. At the population level of smaller cells in all layers there was no suppression of activity but instead supra-granular hyper-excitation as in the large cells, suggesting that the smaller neurons revert to a new hyper-
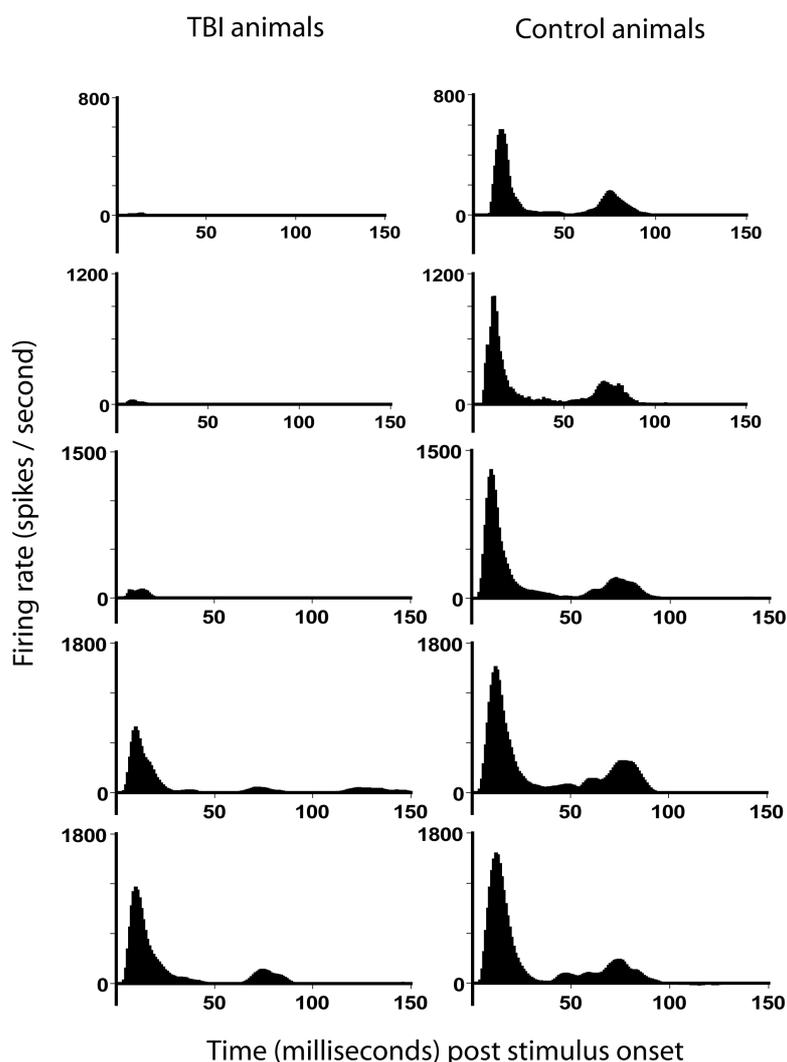
Figure 3. Distance-dependent suppression of neuronal activity 24 hours post Impact injury. *The panels show the population response, plotted as the Grand Peri-Stimulus Time Histogram of firing rate with time from stimulus onset, in TBI animals or Sham control animals. Each row presents a Grand PSTH for a particular cortical lamina: L2 = layer 2, taken as 150-300 μm from the cortical surface; U3 = Upper layer 3, taken as 350-500 μm from the cortical surface; D3 = Deep layer 3, taken as 550-700 μm from the cortical surface; L4 = Layer 4, taken as 750-1000 μm from the cortical surface; and L5 = Layer 5, taken as 1100-1400 μm from the cortical surface. The Grand PSTHs for a layer were generated by averaging the firing rate of all cells and clusters in that layer across all animals in a particular test condition (TBI or Sham). Data averaged from a total of 7 TBI and 6 Sham surgery animals. The stimulus used to generate these Grand PSTHs was a trapezoid stimulus with an onset ramp of 400 mm/s, a hold phase of 20 ms, and a fall ramp phase of 40 ms.*

excitable set point following the shock wave impact. Peri- and post-stimulus inhibition is seen in the population responses, suggesting that inhibitory input (at least from some interneuron populations) remains intact.

Different mechanisms are likely responsible for long-term and short-term sensory cortex hyper-excitability

Hyper-excitability is seen in supra-granular large cells immediately after induction of diffuse TBI and 8 weeks later and it would be parsimonious to assume that the latter simply reflects the former. However, in long-term TBI, the hyper-excitation was revealed only by complex

naturalistic whisker motions that mimic natural behaviours (see Alwis *et al.*, 2012[73] for details) not by simple trapezoid whisker deflections. In contrast, our data show that immediate post-TBI supra-granular large cell hyper-excitation was found only for simple trapezoid deflections of the whiskers. This is an intriguing difference and we postulate that the immediate post-TBI effects reflect a selective release of the supra-granular large cells from inhibition exerted by small cells which have become suppressed through all cortical layers by a stress wave from the impact force. However, by 8 weeks post-TBI the small cells have recovered and in fact exhibit hyper-excitation, much like the large cell supra-granular hyper-excitation at
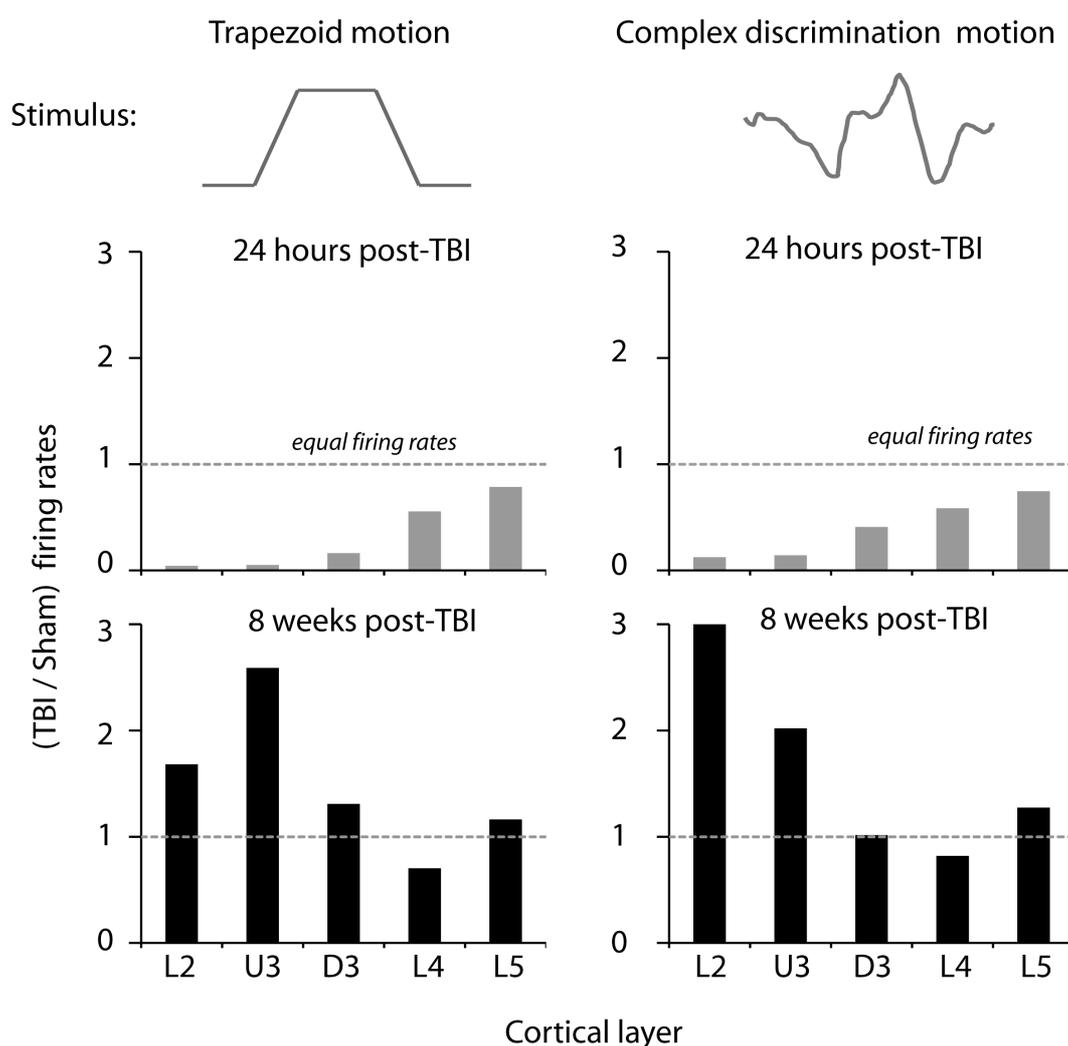
Figure 4. Comparison of the short term and long term changes in firing rates after traumatic brain injury. *The panels show the ratio between the mean peak firing rate in TBI animals to the mean peak firing rate in Sham surgery control animals tested at the same time point post TBI. A ratio of 1 indicates that firing rates in the two groups were the same. Each column of panels is analysis of data obtained with one stimulus type, which is shown above the column of panels. The left column presents data obtained with a simple trapezoid whisker deflection and the right column presents data obtained with a more complex whisker motion that mimics the motion of the whiskers observed across a rough surface in rats trained to discriminate a rough from a smooth surface (see Morganti-Kossmann et al., 2002[68] for details). The top row of panels presents effects seen in animals tested 24 hours post-induction of injury and the bottom row of panels presents effects seen in animals tested 8-10 weeks post-induction of injury. In the panels each bar presents data for a cortical layer indicated in the abscissa labels at the bottom (L2 = layer 2; U3 = Upper layer 3; D3 = Deep layer 3; L4 = Layer 4; and L5 = Layer 5; layers defined in depth terms as detailed in Figure 3 legend). Note that 24 hours post-TBI there is a depth-dependent suppression of responses in TBI animals (n=7) relative to their Sham surgery controls (n = 6), with responses progressively improving towards normal with increasing depth. In contrast, 8 weeks after TBI, there is a massive hyper-excitation to sensory stimulation in TBI animals (n = 16), in the two uppermost layers, near-normal responses in D3 and L5 and a small suppression of responses in the input layer 4, when compared with Sham surgery controls (n = 14).*

this stage. This hyper-excitation must reflect some permanent change, perhaps as a result of increased presynaptic output, increased postsynaptic sensitivity or reduced inhibitory input. In Layer 5 of mouse neocortex, axon regeneration has been shown to occur 28 days post-TBI,[124] and this may also play a role in the effects we see in long-term TBI. Overall, these studies support a shift in the

excitation/inhibition balance in cortex towards increased excitation, manifesting early after injury, and persisting for many weeks.

Sensory cortical response changes have also been suggested to occur through sub-cortical changes,[12,38] which may lead to increased cortical activation.[125,126] However, the general absence of changes in layer 4 responses post-

TBI in our study (at least in the long-term), and the absence of any timing changes in supra-granular layers where hyper-excitation did occur, suggests that our effects are unlikely to be due to changes in thalamic input to cortex.

Complete loss of cortical inhibition is not needed to account for the effects we report. We observed cortical hyper-excitation in the presence of stimulus-driven inhibition in TBI cells. In auditory cortex, cortical inhibition is differentiated into surround and within-field inhibition (arising outside and within the neuron's excitatory response area, respectively; *c.f.* Rajan 2001[127]) and only the former is affected in peripheral injury-induced cortical change.[128] Then, loss of surround inhibition resulted in stronger responses even to stimuli from within the response area, despite preservation of in-field inhibition.[128] This is consistent with our finding of stronger responses to stimuli applied to the principal whisker of the neurons under study (*i.e.*, to stimuli from within the response area of the barrel cortex neurons) while still showing in-field inhibition. In auditory cortex, surround inhibition shapes responses predominantly to complex stimuli[127] and this may account for the fact that in our impact/acceleration TBI model, long-term hyper-excitation was predominant to complex whisker movements but did not occur for simple trapezoid deflections of the whiskers.

The persistent sensory (whisker)-related changes we describe could well correlate with persistent diffuse brain injury-related hypersensitivity to light, sound and touch in humans, as described earlier, and to persistent sensory deficits specific to processing of complex sensory cues. If the long-term effects are due to permanent loss of surround inhibition then, given the role of cortical surround inhibition in shaping responses to complex stimuli,[127] it would be difficult to discriminate between stimuli, especially complex stimuli, in long-term TBI. Our results suggest that human studies using complex, naturalistic stimuli should better reveal the full extent of human sensory processing deficits post-TBI than simple threshold or detection stimuli, and this can be linked to supra-granular sensory cortical changes.

Changes in cortical excitability in other forms of brain injury

Increases in cortical excitation are commonly seen after different types of cortical injury,[129] and are thought to be mainly due to the loss or diminished activity of inhibitory neurons,[130] followed by secondary injury pathways which exacerbate the excitation/inhibition imbalances through mechanisms such as excitotoxity and ionic imbalances causing increased glutamate release,[131] down-regulation of the K^+-Cl^- co-transporter 2 which normally contributes to GABA-mediated inhibition,[119] decreased expression of inhibitory post-synaptic receptors,[132] or decreases in inhibitory synapses.[133] Decreased GABAergic inhibition plays an important role in epileptogenesis, with a concurrent increase in excitatory activity, giving rise to spontaneous epileptiform firing 2-3 weeks post-injury.[134] The activation of alternative cortical

pathways can occur following stroke through circuit reorganization,[135] which is known to occur during periods of cortical plasticity where inhibitory activity is reduced,[136] suggesting the reorganization of cortical pathways surrounding the injured area. Cortical ischemia, as occurs during ischemic stroke, also results in impaired inhibitory neuron activity, shifting the balance towards increased excitation,[137] as has been confirmed in electrophysiological studies of stroke, showing increased cortical excitation and alterations in synaptic activity.[138]

Finally, it is worth noting that sensory processing deficits and hyper-sensitivity to sensory stimuli may contribute significantly to deficits and impairments in high-order cognitive processes and motor function in other brain disorders such as schizophrenia, autism and Fragile X syndrome. Then the excitation/inhibition imbalances we find in sensory cortical processing in TBI may also apply to forms of brain injury[139-142] and may underlie long-term deficits in cognition in many brain disorders.

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