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CHAPTER 10

Brain Injury and Vulnerability to Psychopathology

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HISTORICAL CONTEXT

The 1848 accident incurred by railroad worker Phineas Gage is legendary in psychology and neuroscience, and is described commonly in introductory textbooks. Gage attained fame after surviving an extraordinary accident in which an explosion propelled a 3-foot-long iron rod through the frontal portion of his skull and brain. Merely surviving such an accident is uncommon, but more remarkable was his apparent recovery of memory, communication, and most other basic mental functions. However, reports from those close to Gage indicate that the injury conferred permanent changes to his personality, resulting in self-destructive and socially inappropriate behaviors stemming from poor judgment. As indicated by his friends, he was "no longer Gage" (see Kotowicz, 2007, p. 117). Continued fascination with this story over the past 150 years follows from its demonstration that the brain is responsible for fundamental aspects of our individuality. This story illustrates the importance of brain function for psychological health, and the brain's sensitivity to acute trauma.

TERMINOLOGICAL AND CONCEPTUAL ISSUES

Gage's story describes an instance of open head trauma. More recently, scientists have gained increased understanding of the consequences of traumatic force that occurs without skull penetration—referred to as *closed head injury*. Closed head injuries and their sequelae continue to be a prominent focus of medical research. This is especially the case for mild head injuries, commonly known as *concussions*. A concussion is usually defined as neurological impairment caused

by biomechanical strain on central nervous system (CNS) tissue. As McCrory et al. (2009) note, a concussion occurs as a result of "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces" (p. 37). However, the term *concussion* is often used inconsistently among clinicians to refer to varying severities of brain injury. When children are injured, terms such as *concussion* may be used to ease parental concern, with the implication of a lack of lasting consequences (Dematteo et al., 2010).

Despite the lack of formal definition, concussions are usually diagnosed when symptoms are observed in one or more of the following domains: (a) cognitive—including confusion, poor concentration, inability to follow directions or answer questions, amnesia, and/or loss of consciousness; (b) medical—including headaches, nausea and/or vomiting; (c) sensory—including dizziness, poor coordination, and/or loss of balance, alterations in vision or hearing (e.g., seeing stars or hearing ringing); and (d) psychological—including irritability, changes in personality, and/or context-inappropriate emotions (McCrory et al., 2005). Merritt and Arnett (2014) found that symptoms from the commonly used Postconcussion Symptom Scale (PCSS) load on four distinct factors involving cognitive, affective, physical, and sleep symptoms. Interestingly, one of the most common and often debilitating postconcussion symptoms, headache, does not load clearly on any factor.

Concussions were long believed to be transient physical states with complete resolution of symptoms expected within three months. Thus, it was believed that no permanent changes in brain structure, function, or behavior were incurred by concussion victims (Gaetz, Goodman, & Weinberg, 2000). However, more recent research indicates that detrimental effects can persist for many individuals for extended periods of time, even in cases classified as mild (see Slobounov, Sebastianelli, & Hallett, 2012; Yeates, 2010). Some evidence also suggests that impairment can increase rather than decrease in weeks following injury (Scherwath et al., 2011). Some research also shows that EEG abnormalities can persist weeks after clinical symptoms subside (Slobounov et al., 2012). Thus, full brain recovery may take longer than indicated by self-reported symptoms. Importantly, detrimental effects of mild head injuries are extended and exacerbated when such injuries are experienced repeatedly. Repetitive head injuries are common among both amateur and professional athletes, from childhood through adulthood.

High-contact sports such as football, soccer, and hockey, where head-to-head contact occurs between athletes, and where the head may hit the ground or strike a ball, are associated with high concussion rates (Delaney, Puni, & Rouah, 2006). Consequently, organized sports have become a focus of both research and policy developments with regard to brain injury. In 2009, the Zackery Lystedt Law (2009) (Federal House Bill 1824) was passed, which prohibits young athletes from returning to play after a suspected concussion without approval from a medical professional. This law follows in part from evidence that concussions result in metabolic changes that temporarily enhance susceptibility of the brain to further

damage. Unfortunately, recent neuroimaging research suggests that resolution of these metabolic changes may not coincide with remission of cognitive symptoms or recovery time (Slobounov et al., 2012; Vagnozzi et al., 2008). Considerably more work is needed before more accurate decisions can be made about when vulnerability subsides.

In addition to traumatic head injury, the brain is susceptible to insults from other sources, most notably teratogenic substances (i.e., substances ingested by children or pregnant mothers, which affect the developing brain; see Chapter 9 [Doyle, Mattson, Fryer, & Crocker]), and insufficient supply of oxygen (hypoxia) or blood flow (ischemia). The brain may be especially vulnerable to these influences prenatally. In particular, hypoxia and ischemia result in extensive cell death (see Ment, Hirtz, & Huppi, 2009; Vannucci, 2000), although behavioral and psychological consequences are not specific or well understood. In this chapter, we review basic brain injury mechanisms, discuss specific developmental aspects of brain injury, and consider how injury contributes to the development of psychopathology.

PREVALENCE

Brain injuries occur most often among children between ages 0 and 4 years, and among adolescents between ages 15 and 19 years (Faul, Xu, Wald, & Coronado, 2010). Children between ages 5 and 9 years are less likely to sustain injury (Toledo et al., 2012). Each year an estimated half million children are brought to emergency rooms for treatment of traumatic brain injury (TBI), of whom less than 1% die. An unknown number of additional individuals sustain injuries that are unreported and receive no medical attention (Faul et al., 2010). Abuse is a common cause of head injuries among infants and toddlers, representing an estimated 22% of all TBIs among children between ages 0 and 3 years (Leventhal, Martin, & Asnes, 2010). Factors that result in even mild levels of oxygen desaturation—including medical conditions such as congenital heart disease, sleep-disordered breathing, and severe or poorly treated asthma, as well as accidents such as near drownings or carbon monoxide poisoning—can also result in significant cell death (Bass et al., 2004; Hori, 1985). However, such injuries are difficult to quantify and may go unrecognized in mild cases, making occurrence rates difficult to estimate.

In addition to age, other individual differences are also associated with susceptibility to brain injury. Rates of occurrence are higher among males than among females, and among those of low socioeconomic status (Bruns & Hauser, 2003; Faul et al., 2010; Toledo et al., 2012). Researchers who reviewed medical charts across more than 70 hospitals found that children who are impulsive, including those with attention-deficit/hyperactivity disorder (ADHD), are more likely to sustain injuries to all areas of the body, with the head being no exception. In this study, children with ADHD were also more likely to sustain severe injuries (DiScala, Lescohier, Barthel, & Li, 1998). Some have suggested that the apparent link between ADHD and head injury is due in large part to poor parental supervision commonly experienced by externalizing children (Schwebel, Hodgens, & Sterling, 2006).

Furthermore, although impulsivity is highly heritable (see Chapter 6 [Neuhaus & Beauchaine]), child-specific environmental factors are better predictors of head injury than either genetic or family environmental factors, suggesting little support for a heritable "injury/accident proneness" trait among children (Ordoñana, Caspi, & Moffitt, 2008). Adeyemo et al. (2014) conducted a recent meta-analysis of the mild Traumatic Brain Injury (mTBI)-ADHD relation among over 3,000 mTBI patients and almost 10,000 controls. They found an association between ADHD and mTBI, with a relative risk ratio of 2.0, which indicates that an individual with ADHD has two times the risk of mTBI compared with controls. For studies in which ADHD was present prior to mTBI, there was no association between the two variables. In contrast, for studies in which ADHD emerged after mTBI, a significant relation was found, with a pooled relative risk of 2.2. This finding supports the contentious suggestion that ADHD does not confer vulnerability to mTBI; rather, it is sometimes an adverse sequela of mTBI. It is important to note that other studies have failed to report such findings (see Davidson, 1987; Olsson, Le Brocque, Kenardy, Anderson, & Spence, 2008). Debate continues regarding impulsivity as a risk factor for head injuries, including whether head injuries and externalizing behaviors are multifinal consequences of other environmental risks.

ETIOLOGICAL FORMULATIONS

As noted above, causes of brain injury include accidental trauma (e.g., falls, car accidents, bicycle accidents, sports collisions), nonaccidental trauma (e.g., child abuse), and hypoxic-ischemic events (e.g., pregnancy and birth complications, infections, damage secondary to trauma). Research over the past several decades highlights that brain injuries can occur at any time during development and that multiple causes of injury can result in similar types of brain damage (signifying equifinality). Animal studies and postmortem studies with humans, along with advanced neuroimaging techniques, have helped elucidate mechanisms through which brain injuries and related impairments are effected.

In sections to follow, we focus on the most common and most basic factors that result in brain cell death—trauma and hypoxia—and we describe neuroimaging methods that can detect various types of brain injury, and identify causes of cell death.

Mechanisms of Brain Injury

In this section, we discuss two key mechanisms of brain injury, trauma and hypoxia.

Trauma. Traumatic brain injury is defined as a change in brain function that manifests as confusion, altered level of consciousness, coma, seizure, acute sensory or motor neurological deficit, neuropsychological deficit, or behavioral change, resulting from any blunt or penetrating force to the head (Bruns & Hauser,

2003). TBI occurs when rapid deceleration of the brain against the bony inner surface of the skull produces tissue compression, resulting in neuronal and vascular damage (Finnie & Blumbergs, 2002). The nature of mechanical forces applied to the head produces different types of tissue damage, which are often classified as focal or diffuse (Gennarelli & Meaney, 1996). Focal tissue damage occurs most often in injuries that result from translational forces applied along the linear axis of the brain (Yeates, 2000). Under conditions insufficient to penetrate the skull, such force results in a localized deformation of the bone and compression of underlying tissue (Gennarelli & Meaney, 1996). When the brain compresses against the skull, small hemorrhages develop on its gyral surfaces, which cause a contusion or focal tissue damage (Finnie & Blumbergs, 2002). Such injuries also result in contrecoup contusions, defined as compressive tissue damage at regions remote from the initial contact point. This occurs when a force applied to the head causes the brain to rebound and contact the skull a second time at a point opposite the initial injury (Gennarelli & Meaney, 1996). These types of injuries can result in significant tissue damage, most commonly without loss of consciousness (Gennarelli & Meaney, 1996). Given the degree of tissue damage that can occur without loss of consciousness, unconsciousness is a poor surrogate for radiological and/or neuropsychological assessments (Schutzman & Greenes, 2001). This consideration is reflected in recent updates to sports concussion grading systems, in which post-concussion self-reported symptoms have taken on an increasingly prominent role in defining severity, above and beyond issues relating to loss of consciousness per se (Arnett et al., 2014).

In contrast to focal damage caused by translational injuries, diffuse damage results from rotational forces, producing angular movement around the brain's center of gravity. This damage occurs when the head strikes against a broad object, such as the interior of a car, diffusing the force across the surface of the skull (Gennarelli & Meaney, 1996). Rotational force produces a shearing strain on the brain, tearing axonal tissue. By destroying axons, both afferent and efferent activity may be interrupted in any brain region. Destruction of axonal communication between and across regions can produce functionally similar impairments as those associated with direct focal damage to the disrupted region. For instance, a disruption in the connection between the frontal cortex and subcortical structures can produce frontally mediated impairment without observable damage to the frontal lobe (Schnider & Gutbrod, 1999). In fact, axonal damage is frequently undetectable by standard neuroimaging protocols and thus requires advanced imaging techniques such as volumetric analysis and diffusion tensor imaging (DTI) (Ashwal, Holshouser, & Tong, 2006; Van Boven et al., 2009). Wäljas et al. (2015) recently reported that a high proportion (about 50%) of their mTBI sample showed microstructural abnormalities in the brain, as detected by DTI, within about three weeks postinjury, compared with only about 12% of controls. Because of disrupted

connections between brain areas, these types of injuries often lead to widespread damage and can affect deeper anatomical structures than those related to focal contusions.

Regardless of the form of injury, TBI severity is most commonly classified into categories of mild, moderate, or severe based on acute neurological impairment using the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974). Past estimates of hospitalized brain injured patients indicate that as many as 80% suffer injuries classified as mild based on GCS ratings (Kraus & Nourjah, 1988). Mild injuries can include loss of consciousness, concussive symptoms, and need for short-term hospitalization, but they may also present with sequelae mild enough to be dismissed by the patient (Gabriel & Turner, 1996; Rimel, Giordani, Barth, Boll, & Jane, 1981). Although clinical neuroimages may appear normal, suggesting no lasting damage, diffusion imaging studies with children and adolescents reveal microscopic damage (see Ashwal, Wycliffe, & Holshouser, 2010; Chu et al., 2010). Interestingly, Wilde et al. (2008) found that even among adolescents with normal GCS scores (i.e., 15) and normal CT scans, microstructural brain abnormalities were detected by DTI within 6 days postinjury.

Acquisition of small lesions resulting from mild injuries may be especially dangerous if they accumulate over time through repeated injury (Collins et al., 2003; Prins, Hales, Reger, Giza, & Hovda, 2010). In addition to primary effects of damage in response to biomechanical strain placed on tissue, secondary injuries frequently evolve from brain trauma. Edema, or swelling, often occurs at the site of focal injuries, increasing intracranial pressure and restricting blood flow, which leads to metabolic failures, resulting in cell death (Bigler, 2001b). This can lead to apoptosis, or signaling of one cell to induce death in neighboring cells. Secondary brain injury in response to trauma develops over time and can occur among those whose injuries are initially classified as mild and whose clinical evaluations in the immediate aftermath of the injury appear normal (Schutzman & Greenes, 2001). Because of the extent of secondary injuries, tissue damage is often more global than local. Studies of both children and adults indicate that reductions in total gray and white matter follow even mild injuries, and they appear to increase linearly with injury severity (Bigler, 2001a; Wilde et al., 2005).

Hypoxia. As noted above, hypoxia refers to a reduction in the supply of oxygen necessary for normal cellular function, and can occur through both respiratory and circulatory failures (Nyakas, Buwalda, & Luiten, 1996). Hypoxia leads to brain damage through both acute and protracted pathways. Acute reduction in oxygen inhibits metabolic processes in cells and results in release of neurotransmitters with excitotoxic effects (Golan & Huleihel, 2006). This cytotoxic process then induces a stress response that propagates chemical signaling of the self-destructive process known as apoptosis. Extended activation of

programmed cell death can occur up to several weeks beyond the original hypoxic insult. Accumulation of cell loss over these several weeks is often what leads to behavioral deficits (Golan & Huleihel, 2006). Although research has focused on medical interventions that may arrest this process and alleviate damage induced by acute hypoxic events, such procedures vary widely in their use, often with uncertain clinical utility, particularly for pediatric patients (see Morrow & Pearson, 2010).

Hypoxia that occurs in conjunction with a variety of medical conditions can cause adverse neurological effects (Bass et al., 2004). However, the majority of hypoxic events occur pre- and perinatally. Consequently, pre- and perinatal effects have dominated the study of hypoxia, with far less attention paid to effects of hypoxic events later in life. A common correlate of compromised pregnancies, hypoxia can result from a variety of causes including premature birth and placental insufficiency (Vannucci, 2000). Hypoxia can also follow from restricted blood flow to the umbilical artery, which occurs during episodes of maternal alcohol consumption (Mukherjee & Hodgen, 1982) and smoking (Socol, Manning, Murata, & Druzin, 1982). In cases of prenatal hypoxia, infants are often of low birth weight for their gestational age, a gross indication of maldevelopment (McClure, Peiffer, Rosen, & Fitch, 2005). In addition to prenatal damage, hypoxia can also occur during the birthing process from restricted oxygen flow to the fetus during a prolonged or complicated delivery, resulting in respiratory difficulties requiring resuscitation. Hypoxic damage ranks among the top 10 causes of death among neonates (Martin, Kochanek, Strobino, Guyer, & MacDorman, 2005), and is a common complication for babies born preterm. The incidence of preterm birth was 12.3% in the United States in 2003 (Martin et al., 2005). Fortunately, in recent years, survival rates have been increasing, leading to decreases in medical complications, negative neurological sequelae, and adverse cognitive effects (Baron & Rey-Casserly, 2010).

Regions of tissue damage and resultant behavioral implications following hypoxia depend on a wide range of factors, which complicates clinical efforts to generate prognoses (Golan & Huleihel, 2006). Factors such as developmental maturation of neural tissue, duration and degree of hypoxic exposure, and degree of neuroprotective factors intrinsic to an individual are difficult to identify and quantify in clinical practice. Thus, sequelae of hypoxia are variable and range from mild impairments in cognition and behavior to deficits in motor coordination and development of cerebral palsy. If ischemia also occurs, more severe atrophy of brain regions including the motor cortex, hippocampus, and striatum may occur (Decker & Rye, 2002). When extreme and overt compromise is evident—resulting in such conditions as motor disabilities, cerebral palsy, and epilepsy—the extent of damage may be revealed with neuroimaging techniques. Using magnetic resonance imaging, white matter damage is the most commonly identified pathology among infants who suffer hypoxia prenatally, with additional reductions in overall cortical gray matter (Robinson, 2005; see Ment et al., 2009).

However, more subtle variations in neurochemical functions that affect cellular communication also occur in response to hypoxia. These may be insufficient to produce gross structural damage. For instance, researchers have found decrements in dopamine receptors in the striatum following experimental induction of hypoxia/ischemia, despite normal structural appearance (Zouakia, Guilloteau, Zimmer, Besnard, & Chalon, 1997). In fact, striatal cells are the most vulnerable to cell death incurred by mild hypoxia (Rothstein & Levison, 2005). Such insults may result in psychological and behavioral disturbances, including ADHD (Gatzke-Kopp, 2011), even in the absence of marked neurological dysfunction (Nyakas et al., 1996). These findings are consistent with theories identifying mesolimbic, striatal dopamine deficiency as a primary etiological contribution to the development of ADHD-related symptoms (Beauchaine & McNulty, 2013; Gatzke-Kopp, 2011; Gatzke-Kopp & Beauchaine, 2007; Sagvolden, Johansen, Aase, & Russell, 2005). Low-grade hypoxia may also contribute directly to development of psychopathology. In animal experiments, intermittent hypoxia results in attenuation of extracellular dopamine in nigrostriatal regions, which is implicated in behavioral hyperactivity and increased responding to novelty (Decker, Jones, Solomon, Keating, & Rye, 2005). Interestingly, evidence suggests that male and female brains differ in the degree of vulnerability to ischemia/hypoxia induced damage, with females showing less severe pathological outcomes (Hurn, Vannucci, & Hagberg, 2004; see Anderson, Spencer-Smith, & Wood, 2011).

Advances in Neuroimaging of Pediatric TBI

The most common clinical imaging techniques include computed tomography (CT) and magnetic resonance imaging (MRI). Because MRI does not require radiation exposure, it is advantageous when repeated scans are necessary. MRI volumetric analysis identifies both gray and white matter total and regional volume loss, which correlate with injury severity (Levine et al., 2008; Van Boven et al., 2009). However, findings from the past 5 to 10 years, in which the use of advanced imaging techniques has become increasingly common, suggest that volumetric MRI may be insufficiently sensitive to neuronal damage associated with mild head injuries.

Structural measures such as susceptibility-weighed imaging (SWI) and diffusion tensor imaging (DTI) allow for increased sensitivity to hemorrhagic and axonal injury, respectively (Van Boven et al., 2009). SWI capitalizes on different magnetic susceptibilities of discrete tissue types, and can be calibrated to preferentially enhance sensitivity to detection of blood (Van Boven et al., 2009). SWI can identify 4 to 6 times as many microhemorrages as standard clinical imaging protocols and is useful in predicting neurologic and neuropsychiatric outcomes (Ashwal et al., 2010). DTI measures diffusion of water molecules and is thought to index integrity of white matter tracts. DTI is sensitive to microstructural abnormalities, and is especially useful in mild TBI, for which structural abnormalities may not be detected with standard imaging protocols. However, this method is nonspecific,

and abnormalities may represent a variety of conditions, including axonal sheering, demyelination, inflammation, and edema (Van Boven et al., 2009). Regardless of etiology, changes in diffusivity identified by DTI predict working memory and executive function deficits among children (Wozniak et al., 2007). In fact, in assessing diffuse prefrontal injury, DTI may be more predictive of neurological outcomes than traditional MRI techniques (Oni et al., 2010).

Key indices for DTI include fractional anisotropy (FA), an index of diffusion restriction, and apparent diffusion coefficient (ADC), a measure of magnitude of diffusion. Higher FA and lower ADC are typically associated with greater brain integrity. This relation can reverse during acute stages of mTBI, a pattern that may relate to acute cytotoxic edema or swelling of the brain, as indicated in a small sample of 12 adolescent mTBI patients (Wu et al., 2010). Compared with 11 controls, mTBI patients in an acute phase following injury (mean ~3 days, range = 1–6 days) exhibited higher FA and lower ADC. Also of interest, FA was correlated negatively with verbal memory performance in the mTBI group, but positively in the control group. Thus, in the acute phase following injury, the meaning of DTI metrics can be different than among healthy controls and among those who are in the more chronic phase following injury.

Other measures, such as magnetic resonance spectroscopy (MRS), may be better suited for detecting metabolic changes in cell function related to brain injury and vulnerability. MRS allows for assessment of metabolites that mark injury, even in clinical scans that are deemed "normal." Among children, altered metabolite ratios (i.e., lower *N*-acetylaspartate (NAA)/creatine (CR), lower NAA/choline (Cho), higher Cho/Cr) are related to poorer neurological and neurobehavioral outcomes (see Ashwal et al., 2010).

Advances in statistical analyses have also provided better understanding of the sequelae of damage, but only recently have these methods been used with children. Functional connectivity analyses provide information about interrelations between brain regions rather than simple independent levels of activation within given regions. Functional connectivity can refer to any correlational measure of regional activation but is most often used to refer to correlations in blood-oxygen level dependent (BOLD) activation either during task or resting-states. It provides an indirect measure of coordination between brain regions without assuming anatomical connectivity (Fox & Raichle, 2007). To date, functional connectivity studies with children are sparse. Most existing investigations include adolescents, presumably because they are easier to scan. However, in one study, task-related functional connectivity between Wernicke's area and other bilateral language areas during passive listening was stronger for children born preterm than for controls, suggesting a broader and less specialized functional brain network for language processing among preterm children (Gozzo et al., 2009).

Functional neuroimaging studies are limited in the child/adolescent literature on mTBI. In one study, Slobounov et al. (2010) found that, compared with matched controls, concussed athletes showed increased activation on fMRI in the right parietal,

right dorsolateral prefrontal, and right hippocampal regions. Such findings have sometimes been replicated in adult samples (Mayer, Bellgow, & Hanlona, 2015). This pattern of increased brain activation following injury may suggest compensation. However, across a broader literature that includes both children and adults, some studies show evidence for hypoactivation in certain brain regions following mTBI (Mayer et al., 2015). At this stage of knowledge, there is no clearly integrated theory that can account for apparently contradictory findings in which some studies show increased brain activation in mTBI and others show decreased activation. In the section below on "Brain Injury and The Frontal Lobes," we discuss some issues relating to the possible importance of site of injury in functional outcome.

Resting-state patterns in brain functional integration, or "default mode" networks, also change across development (Fair et al., 2009). Abnormalities in resting-state connectivity have been identified among children born preterm (Damaraju et al., 2010), and among adults who sustain TBI (Johnson, Zhang et al., 2012). Advanced imaging techniques have allowed for greater detection of injury and predictive utility in pediatric populations. These measures are not only more sensitive to changes that result from both primary and secondary injury, but also, in conjunction with traditional imaging modalities, hold promise for better detection of pediatric brain injury (Ashwal et al., 2006).

DEVELOPMENTAL CONSIDERATIONS

Injuries sustained by children may confer different vulnerabilities than similar injuries sustained by adults. Rodent models demonstrate that the same dopamine-depleting lesions that produce severe motor impairment in mature rats may result in motor hyperactivity when induced in juvenile rats (Davids, Zhang, Tarazi, & Baldessarini, 2003). Among humans, children who experience frontal lobe damage exhibit greater loss of psychosocial function than adults who sustain similar injuries (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999).

Developmental factors affect the nature and degree of injury sustained and the degree of functional recovery likely to follow. Greater neck strength can mitigate kinematic responses to head impact across all planes of motion in both pediatric and adult athletes (Eckner, Oh, Joshi, Richardson, & Ashton-Miller, 2014). Children's relatively large heads and weaker neck muscles therefore increase their vulnerability to rotational movements implicated in diffuse axonal injuries. Furthermore, greater flexibility of their skulls allows force to be distributed over a greater surface area, favoring diffuse over focal injuries (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005).

The developmental state of tissue is also implicated in the extent of damage that mechanical forces have on the brain. More than any other organ in the human body, brain development is far from complete at birth, with developmental changes continuing well into the postnatal period, through adolescence and early adulthood (Johnson, 1999; Nowakowski & Hayes, 2002; Sowell, Thompson, Holmes,

Jernigan, & Toga, 1999). Developmental changes in brain maturation also differ across tissue types. White matter develops its characteristic appearance after birth, as axons connecting cells across anatomical regions become myelinated (Andersen, 2003). Myelination occurs rapidly in the first few years of life (McKinstry, 2011), but continues throughout childhood and adolescence (Giedd et al., 1999). Lower levels of axonal myelination among children increase susceptibility to shearing strain, rendering children vulnerable to diffuse injuries (Lea & Faden, 2001). Furthermore, hypoxia can induce failure of myelination (see Ment et al., 2009).

In contrast to white matter development, gray matter development includes processes that refine synaptic relationships between neurons. Immature brains contain excess neurons. Based on an individual's experience, neurons that are used regularly form connections with other neurons to develop efficient circuits, whereas neurons that are not used are eliminated. Despite pruning, the brain continues to grow through early childhood. This growth is due in part to arborization, or branching of neurons to increase the number of neighboring cells with which they communicate. Gray matter develops at different rates across each of the four lobes (Giedd, 2004), with regions of the frontal lobe continuing to develop well into adulthood (Diamond, 2002). Gray matter in children is more susceptible to secondary injuries following trauma, such as edema (Aldrich et al., 1992). This susceptibility is likely to be related to immaturity of neurochemical receptors in young brains, increasing vulnerability to excitotoxic damage associated with hypoxia and contributing to extensive apoptotic cell death (Lea & Faden, 2001).

The relative immaturity of the brain at birth is also an asset in human development because the brain remains plastic. Structure of neural tissue is not determined entirely by genetic or chemical signals that take place during development. Experience-dependent specialization also emerges (Johnson, 1999). Thus, when structure is compromised through injury prior to specialization of cortical tissue, alternate brain regions may assume functions of lost tissue. For example, portions of the auditory cortex may respond to visual stimuli when the visual cortex is damaged prior to neuronal specialization (Johnson, 1999). However, despite the remarkable compensatory ability of younger brains, there are clear limits to plasticity, and functional recovery is often far from absolute. The diffuse nature of damage in TBI may limit healthy tissue available for organizational compensation. Furthermore, when recovery occurs for some functions, it may be at the expense of acquiring other abilities (Luciana, 2003). Among rodents, early brain tissue damage results in neural organizational compensations that allow for recovery of motor control not seen in animals damaged in adulthood, yet diminished cognitive functioning is also observed (Kolb & Gibb, 2001). Brain plasticity in childhood therefore may not predict full recovery. Rather, extensive brain damage may prevent acquisition of new skills necessary to traverse developmental landscapes effectively (see Anderson et al., 2011).

Timing of TBI has significant implications for vulnerability to poor outcome. Early damage often carries a substantial cost over the course of development.

Damage to the brain that results in an inability to acquire basic functions may affect wide-ranging higher-order processes that depend on that initial component (Bachevalier & Loveland, 2003; Black, Jones, Nelson, & Greenough, 1998). For example, children who sustain brain injuries prior to age 4 years exhibit worse cognitive and social outcomes than children who sustain injuries just 2 years later (Sonnenberg, Dupuis, & Rumney, 2010). Although younger age at injury is cited consistently as a vulnerability to poor outcome (Anderson et al., 2005), research does not support a linear relationship between age at time of injury and outcome (Crowe, Catroppa, Babl, Rosenfeld, & Anderson, 2012). Rather, the relation between age and outcome is better characterized by a stepwise pattern, with several critical periods of development marking times of increased vulnerability.

Developmentally, the brain is characterized by sensitive periods. In general, *sensitive periods* refers to any developmental epoch during which plasticity is heightened to facilitate skill acquisition across certain brain regions. Damage sustained during peak periods of developmental sensitivity may be most likely to induce long-term deficits (Ewing-Cobbs, Prasad, Landry, Kramer, & DeLeon, 2004). Indeed, damage incurred prior to periods of developmental sensitivity allows time for alternative brain regions to be recruited, whereas damage incurred later allows for preservation of skills that were acquired prior to the injury. A 2012 study comparing intellectual outcome following TBI among four age-at-injury groups (infant, preschool, middle childhood, and late childhood) demonstrated that middle childhood injuries were associated with lower IQ scores across domains and injury severity (Crowe et al., 2012). Thus, middle childhood may be a particularly sensitive period of neural development.

Contradictory predictions offered by increased plasticity versus increased vulnerability are complex; they cannot be accounted for fully by severity or age at injury alone. Anderson, Spencer-Smith, and Wood (2011) proposed a hierarchical model to account for the high degree of variability in outcomes and considerable clinical challenges in prognosis. They suggest that functional and neural recovery from early brain injury is influenced by independent and interacting effects of developmental, constitutional, and environmental factors. Individual differences in biological susceptibility and resilience to injury are also being identified (see below). Furthermore, individual difference factors such as cognitive ability and sex may moderate outcomes. For example, cognitive ability, measured within 3 weeks of injury among children with mild TBI, moderates postconcussive symptoms 3 months later (Fay et al., 2010). In addition, females are at greater risk for postconcussive symptoms after mild TBI, but at the same time may be protected from social skills and processing speed deficits postinjury (see Stavinoha, Butcher, & Spurgin, 2011). Animal research suggests that the less-lateralized female brain may have a greater potential for plasticity and transfer of function between hemispheres after injury. However, other research indicates that male animals show greater neural and behavioral recovery after injury in response to enriched environments (Anderson et al., 2011; Kolb, Gibb, & Gorny, 2000). Finally, environmental factors

including both interpersonal support and medical intervention also affect prognosis (Anderson et al., 2011).

BRAIN INJURY AND THE FRONTAL LOBES

Regionally, the temporal and frontal lobes are especially vulnerable to damage (Mendelsohn et al., 1992; Wilde et al., 2005). Susceptibility of these regions is a consequence of their proximal location to the jagged inner surface of the skull (Schnider & Gutbrod, 1999). In addition, these regions readily sustain contrecoup contusions regardless of the initial site of impact (Gennarelli & Meaney, 1996).

Although many brain regions are developmentally stable at adult levels by adolescence, maturational changes in frontal regions continue through adolescence and into early adulthood, supporting continuing emotional and cognitive development during this age range (Sowell et al., 1999). Given such protracted maturation, prefrontal structures may be vulnerable to effects of injury longer than other anatomical sites. Functions performed by the frontal lobes are critical to mental health, and their compromise is of substantial clinical importance. This anatomical region is frequently divided into dorsal and orbital cortical subregions, which have unique yet interactive psychological functions (Duncan & Owen, 2000). The orbital frontal cortex (OFC) is the ventral-most region of the frontal cortex, whereas the dorsolateral prefrontal cortex (DLPFC) occupies the lateral region above the OFC. These regions maintain extensive reciprocal connectivity with limbic structures.

DORSOLATERAL PREFRONTAL CORTEX

The DLPFC and mid-dorsal cortices respond to a variety of cognitive demands that require problem solving and executive functioning (Duncan & Owen, 2000). The DLPFC operates through a network of interconnected structures including the dorsal caudate, global pallidus, dorsomedial thalamic nucleus, and cerebellum (Heyder, Suchan, & Daum, 2004). Integrity of this network is essential for future planning toward attaining distal goals (Anderson & Catroppa, 2005; Levin & Hanten, 2005). This region is implicated in inhibitory control and the ability to integrate environmental feedback into ongoing behavior to make rapid behavioral changes. These skills are often deficient among individuals who incur frontal brain injuries (Ornstein et al., 2009), with potential long-term consequences including long-term neurodegenerative changes. Keightley et al. (2014) reviewed evidence for volume loss in several brain regions (hippocampus, amygdala, globus pallidus, thalamus, etc.), as well as reduced whole brain volumes and increased cerebral spinal fluid and ventricular space, following TBI in children (Keightley et al., 2014).

Because executive functions are crucial for adapting to changing developmental and environmental demands, early damage to this region may establish cascading effects of initial decrements across multiple domains of function. Such skills begin

to emerge in preschool and undergo rapid development thereafter (Diamond, 2002). Because frontal regions are not well developed among young children, damage is less likely to reveal immediate behavioral deficits, whereas such damage would be detected readily among adults. In adults who sustain TBIs during childhood, executive functioning difficulties are found (Papoutsis, Stargatt, & Catroppa, 2014). In the immediate aftermath of injury among children, executive deficits may be minimal, but may become evident later in development (Eslinger, Biddle, & Grattan, 1997; Bachevalier & Loveland, 2003). In a case study of two individuals who sustained significant orbitofrontal damage before age 16 months, recovery and function appeared very positive in the immediate aftermath of the lesions, and cognitive and motoric development proceeded normally. However, many years later these individuals were brought to medical attention because of significant psychopathological behaviors. Both appeared to be insensitive to punishment, unresponsive to future consequences, and showed extensive impairment in moral and social reasoning (Anderson et al., 1999). DTI assessments with children who incur OFC damage show disruption of the uncinate fasciculus, which connects the orbital frontal cortex to temporal regions and correlates with poor social/behavioral outcomes (Johnson, Juranek, et al., 2011). Increased deficits in comparison to adult-onset lesions indicate impairment in the acquisition of normal social behavior leading to more global dysfunction.

Orbitofrontal Cortex

In contrast to executive function deficits, damage to orbitofrontal regions is associated with deficits in social/emotional functions that are important in interpersonal relationships, such as the ability to read social and emotional cues and the ability to use this information for self-regulatory purposes (Bachevalier & Loveland, 2003). In a recent study, adult survivors of pediatric TBI showed significantly poorer emotion perception than controls (Ryan et al., 2014). Damage in this region is also associated with inability to develop and/or use internal cues of potential punishment to guide behavior (Damasio, Tranel, & Damasio, 1990). Interestingly, behavior and personality deficits associated with damage to this region frequently exist in the absence of overt neuropsychological deficits (Schnider & Gutbrod, 1999).

Hemispheric localization of orbitofrontal lesions is influential in the clinical presentation of symptoms. Lesions localized to the left hemisphere are associated with depressive symptoms, apathy, emotional blunting, and poor planning, whereas right-hemisphere lesions are associated with hyperactivity, disinhibition, socially inappropriate behavior, irritability, and lack of empathy (Schnider & Gutbrod, 1999). When damage extends across both hemispheres, characteristics of both syndromes coexist (Schnider & Gutbrod, 1999).

A number of investigations have also evaluated long-term effects of childhood TBI, which is associated with psychosocial difficulties in adulthood

(Ryan et al., 2015; Scott, McKinlay, McLellan, Britt, & Grace, 2015). In a study of theory of mind among patients who were 6 months post-TBI, those who sustained more severe injuries were more seriously affected than children with mild to moderate TBIs or healthy control participants (Ryan, Catroppa et al., 2015).

GENETICS AND HERITABILITY

In addition to factors such as developmental phase, sex, injury location, and injury severity, individual differences in functional and structural deficits following brain injury may be influenced by genetic factors (Blackman, Worley, & Strittmatter, 2005; see McAllister, 2010, for review). Research addressing genetically mediated differences in susceptibility to postinjury outcome has expanded rapidly over the past decade. Allelic variants of genes associated with cognitive function, and variants of genes that enhance or impede postinjury cellular recovery, moderate outcomes following neurological insult (Dardiotis et al., 2010; Jordan, 2007; McAllister et al., 2008; McAllister, 2010). The latter category has received the majority of attention to date, with a significant emphasis on the apolipoprotein E (ApoE) gene, which has at least three well-characterized allelic variants. Extensive research on the function of the ApoE proteins indicates a role in neurologic repair, with variability between alleles implicated in the degree of neural damage suffered from oxidative, circulatory, and traumatic type injuries over the lifespan (Blackman et al., 2005; Laskowitz et al., 2010).

In contrast to the $\varepsilon 2$ and possibly the $\varepsilon 3$ allele, the $\varepsilon 4$ allele appears less effective in conferring neuroprotection and leads to increased damage due to postinjury inflammation, edema, and excitotoxicity (Aono et al., 2002; Lee, Aono, Laskowitz, Warner, & Pearlstein, 2004; Lynch et al., 2002). Thus, potential for important Gene × Environment (G × E) interactions applicable to neuropsychological function exists. However, given differences between children's developing brains and adult brains, genes may have varying degrees of effects on outcome depending on when injury is sustained (Kurowski, Martin, & Wade, 2012).

Although G × E interactions have begun to be examined in adult TBI samples, research examining ApoE $\varepsilon 4$ in children is relatively sparse. Among investigations that have examined ApoE $\varepsilon 4$ in adolescent samples, inconsistent findings have resulted. Some indicate a neuroprotective function of $\varepsilon 4$ (Blackman et al., 2005; Oria et al., 2005), whereas others suggest that having an $\varepsilon 4$ allele may confer risk for poor outcome following brain injury (Brichtova & Kozak, 2008; Teasdale, Murray, & Nicoll, 2005). Another concluded that the $\varepsilon 4$ allele appears to have little effect on overall outcome (Moran et al., 2009). However, two significant findings were reported: (1) $\varepsilon 4$ allele carriers are more likely to have worse injury severity scores (as indicated by Glasgow Coma Scale) than non-$\varepsilon 4$ carriers, and (2) $\varepsilon 4$ allele carriers display *better* performance on a visual-motor task than non-$\varepsilon 4$ allele carriers (Moran et al., 2009). Finally, a study that examined cerebral perfusion pressure identified a marked discrepancy between brain

swelling postinjury and severity of outcome for children with the ε4 allele (Lo et al., 2009). Despite the lowest degree of cerebral perfusion, children with the ε4 allele evidenced far worse outcomes, whereas the opposite held for children with the ε3 allele. Some of these discrepancies may well pertain to small sample sizes.

In a recent study of collegiate athletes who were mostly within the first week following concussion, Merritt and Arnett (2016) found that those with the ε4 allele reported significantly more symptoms overall than concussed athletes without the ε4 allele. In addition, ε4 allele carriers were more likely to report physical and cognitive postconcussion symptoms compared to the non-ε4 allele group. It will be useful for investigators to replicate such findings in younger-aged samples, tested in the acute phase postconcussion.

Research also indicates the potential for genotypes to interact with environmental trauma exposure in ways that produce specific psychiatric outcomes (see, e.g., Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, 2011). For example, a range of perinatal traumatic factors, many of which may contribute to hypoxic damage in neonates, are associated with later development of schizophrenia (Rosso & Cannon, 2003). Cannon and colleagues (2002) found that a history of fetal hypoxia was associated with a distinct pattern of brain abnormalities visible on MRI in patients with schizophrenia, but not in a control sample. One component of genetic risk for schizophrenia might be heightened sensitivity to hypoxic events. Thus, onset of illness is potentiated particularly for genetically vulnerable individuals who experience hypoxia during neural development (Cannon et al., 2002). In fact, as many as 50% of reported schizophrenia-related genes may be regulated in part by hypoxia/ischemia (Schmidt-Kastner, van Os, Steinbusch, & Schmitz, 2006).

Animal models indicate that these genes are likely to be expressed during development and contribute to vulnerability to schizophrenia. Vulnerability genes that respond to oxidative stress may confer risk by producing defective gene products that would normally subserve neuroprotective functions. Other lines of research have shown that the relation between genetic risk for depression and offspring externalizing behavior was moderated through pregnancy risk (Pemberton et al., 2010). Thus, one mechanism through which genetic risk confers vulnerability to various forms of psychopathology is through susceptibility to injurious influences on neural development.

Dopamine functioning is also highly sensitive to environmental insults such as hypoxia (Gatzke-Kopp, 2011). Changes in dopamine function following hypoxic insults may be especially detrimental for individuals whose dopaminergic function is genetically compromised (McAllister et al., 2005). Although not yet explored in a pediatric samples, in adult TBI, dopamine-related genes (e.g., Catechol-O-methyltransferase (COMT) Val158Met, ANKK1 and the dopamine D2) may play an important role in neuropsychological functioning postinjury (Lipsky, Sparling, Ryan, Xu, & Salazar, 2005; McAllister et al., 2005; McAllister et al., 2008).

CLINICAL CONSIDERATIONS

As the Phineas Gage example makes clear, brain injury can play a causal role in the pathogenesis of psychological disorders by compromising neural systems directly. Changes in behavior and personality are common in response to brain injury as a consequence of the high prevalence of orbitofrontal damage. Children with a history of mild TBI prior to age 5 years are more likely to evidence clinical impairment in adolescence, with a 4.2-fold increase in ADHD, a 6.2-fold increase in conduct and oppositional defiant disorders, a 3.6-fold increase in the development of substance abuse, and a 3.1-fold increase in prevalence of mood disorders (McKinlay, Grace, Horwood, Fergusson, & MacFarlane, 2009). In addition, TBI often compromises social functioning. Research aimed at delineating the nature of such social impairments indicates problems in emotion perception, theory of mind, and identification of irony and empathy (Dennis et al., 2013; Robinson et al., 2014; Ryan et al., 2014).

Although psychological symptoms may develop as a direct result of lesions to a damaged area, brain injury may also contribute to psychopathology indirectly, through exacerbation of preexisting pathologies, or via development of traumatic stress disorders following injury (Middleton, 2001). This observation is especially salient given that factors such as low socioeconomic status and poor family functioning increase risk of sustaining brain injuries (Bruce, 1996). Some research also suggests that brain-injured patients show higher levels of premorbid psychological and behavioral disturbances (Cattelani, Lombardi, Brianti, & Mazzucchi, 1998). Premorbid functioning also contributes significantly to development of adverse outcomes postinjury (Donders & Strom, 2000). Brain injury may also increase stress in family systems, leading to the display of further contextual risk factors for suboptimal recovery and development. Greater family-level distress and caregiver burden are observed among families of children who sustain a brain injury, compared to other injuries that require hospitalization (Stancin, Wade, Walz, Yeates, & Taylor, 2010). High family functioning moderates the relationship between injury and long-term functioning (Gerrard-Morris et al., 2010; Yeates et al., 1997). Young children, ages 3 to 6 years, who sustain mild to moderate head injuries, demonstrate lower social competence postinjury than matched controls who sustain orthopedic injuries (Yeates, Taylor, Walz, Stancin, & Wade, 2010).

Individuals with severe brain injury evidence the worst outcomes regardless of parenting practices, whereas parents are an important influence in children's coping with and compensating for functional impairments resulting from milder brain injuries (Yeates et al., 2010). These findings highlight the importance of postinjury clinical support for parents and the injured child in order to maximize recovery and prepare for behavioral challenges. Brain injuries establish vulnerability, and when such vulnerability is met with environmental risk, the likelihood of developing psychopathology may well be increased.

Identifying effects of brain injury on psychopathological development may also have important implications for treatment. For instance, research suggests that

methylphenidate is less effective when ADHD emerges after traumatic brain injury than when ADHD follows a traditional developmental course (Jin & Schachar, 2004). When brain injury is identified, treatment should focus not only on the child's level of functioning but also on quality of family environment. Treatment programs targeting behavioral symptoms of TBI through a focus on problem solving in the family environment have yielded promising results (Cohen, Heaton, Ginn, & Eyberg, 2012; Wade et al., 2015). Family problem-solving programs are particularly effective for families of lower socioeconomic status (Wade et al., 2015).

Because dysfunctional family systems may already be in place, the potential effectiveness of the family to cope with the injury and contribute to successful recovery is already limited. These factors are especially important given that head injuries may result from abuse or neglect. Unfortunately, assessing the role that head injuries play in the development of psychopathology is extremely challenging because brain injury can be difficult to detect in cases in which it exists primarily at a microscopic or neurochemical level. Furthermore, a long interval between acquisition of injury and onset of psychopathology may obscure causal relations between injury and later behavior. As many as 75% of infants who survive acute perinatal asphyxia are classified as *nonimpaired* because they fail to show neurological indicators of encephalopathic damage in weeks after injury. As noted above, however, impairments in cognitive, memory, and socioemotional behavior are often not evident until later in life, when children fail to meet increasing developmental demands (de Haan et al., 2006). Even mild insults may produce lasting alterations in development, which may take years to recognize (Gronwall, Wrightson, & McGinn, 1997). In addition, even mild brain damage, which can be caused by low-grade hypoxia associated with snoring, may result in reductions in attention and intelligence, even when children score within normal ranges when tested, and are thus overlooked medically (Blunden, Lushington, Kennedy, Martin, & Dawson, 2000). Therefore, careful consideration of potential contributions of brain injury to presenting psychological symptoms should be undertaken so that appropriate comprehensive treatment plans can be developed.

SUMMARY AND CONCLUSIONS

Although children who incur acute brain injuries present and are treated in medical settings, effects of their injuries may be lifelong and include psychopathology. Severe injuries affect multiple domains of functioning and present serious challenges to both children and their caretakers. However, brain injuries can also be subtle, as in mild TBI or hypoxia. Such injuries may be difficult to detect even when they potentiate psychopathology. In addition to environmental and genetic factors that are becoming increasingly well characterized in the development of psychopathology, early brain injury should not be overlooked, particularly as an environmental potentiator of genetic susceptibility (Gatzke-Kopp, 2011). Because injuries can be difficult to detect and their sequelae may take years to manifest, associations between

injury and psychopathological outcomes may be overlooked in clinical practice. However, information about brain injury may be important in informing treatment strategies, and therefore should be assessed. Research aimed at addressing these challenges will improve our ability to assess brain damage resulting from concussions. In the past decade, advances in neuroimaging have allowed for increased detection of microscopic injuries that may cause lasting effects, but these methods have not been readily adopted in clinical practice. Standard neuroimaging protocols and acute neuropsychological testing continue to dominate current postinjury assessments and are used in recommendations for return to play for athletes, even though both yield limited sensitivity in quantifying extent of neurological damage (Ellemberg, Henry, Macciocchi, Guskiewicz, & Broglio, 2009.) Further research on genetics of brain injury may also assist in (a) identifying individuals who are especially vulnerable, (b) characterizing biological processes involved in injury, and (c) developing appropriate pharmaceutical approaches to arresting neurodegenerative processes. The next steps in understanding pediatric brain injury should focus on multidisciplinary, translational research, which capitalizes on recent advances in neuroimaging, behavioral research, and clinical practice (Anderson et al., 2011).

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