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Age, Plasticity, and Homeostasis In Childhood Brain Disorders

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Abstract

It has been widely accepted that the younger the age and/or immaturity of the organism, the greater the brain plasticity, *the young age plasticity privilege*. This paper examines the relation of a young age to plasticity, reviewing human pediatric brain disorders, as well as selected animal models, human developmental and adult brain disorder studies. As well, we review developmental and childhood acquired disorders that involve a failure of regulatory homeostasis. Our core arguments are:

- Plasticity is neutral with respect to outcome. Although the effects of plasticity are often beneficial, the outcome of plasticity may be adaptive or maladaptive.
- The young age plasticity privilege has been overstated.
- Plastic change operates in concert with homeostatic mechanisms regulating change at every point in the lifespan.
- The same mechanisms that propel developmental change expose the immature brain to adverse events, making it more difficult for the immature than for the mature brain to sustain equilibrium between plasticity and homeostasis.

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- Poor outcome in many neurodevelopmental disorders and childhood acquired brain insults is related to disequilibrium between plasticity and homeostasis.

Keywords

Plasticity; homeostasis; neurodevelopmental disorders; childhood-acquired brain damage; age at brain injury; time since brain injury

1. Introduction

This paper considers the role of age in brain and behavioral plasticity. It has been widely accepted that the younger the age and/or immaturity of he organism, the greater the brain plasticity. We term this *the young age plasticity privilege*. Focusing primarily on human pediatric brain disorders, as well as selected animal models, human developmental and adult brain disorder studies, we examine how the idea of a young age plasticity privilege came about; identify historical and current challenges to the young age plasticity privilege; discuss regulatory homeostasis in brain and behavioral function; and review childhood brain disorders that involve a failure of regulatory homeostasis. These issues address the general question, how do plastic change and homeostatic regulation operate over age to shape outcome in disorders of the immature brain?

Our core arguments are:

- Plasticity is neutral with respect to outcome and it is not *designed* to be adaptive. Although the effects of plasticity are often beneficial, the outcome of plasticity may be adaptive or maladaptive.
- The young age plasticity privilege has been overstated, and important evidence shows plasticity to operate in mature as well as immature organisms.
- Plastic change operates in concert with homeostatic mechanisms regulating change at every point in the lifespan.
- The same mechanisms that propel developmental change expose the immature brain to adverse events, making it more difficult for the immature than for the mature brain to sustain equilibrium between plasticity and homeostasis.
- Poor outcomes in many neurodevelopmental disorders and childhood acquired brain insults are related to disequilibrium between plasticity and homeostasis.

1. 1 The term *plasticity*

Plasticity is the capacity of a system to respond to normal or aberrant developmental or lesion-induced changes in the internal or external environments by adopting new, stable, developmentally appropriate phenotypes and/or restoring old phenotypes. The term *plasticity* has deep historical roots (Berlucchi & Buchtel, 2009) ranging from William James, who used the term for changes in neural paths that establish habits (James, 1890), to Ramón y Cajal, who used the term for regenerative capacities of peripheral and central nervous systems (Stahnisch & Nitsch, 2002), and Lugaro (1913), who suggested that chemotropic activities promote new synaptic functions (*la plasticità*).

Even today, the term *plasticity* is used in many different ways (Will et al., 2008) and refers variously to molecular, cellular, neural, or behavioral systems (Cramer et al., 2011) that achieve novel functions (Paillard, 1976; see Will et al., 2008 for English translation and commentary). *Plasticity* may refer to events at a *microlevel* (e.g., the fine-tuning of prewired circuits favoring activation of specific granule cell groups in the olivo-cerebellar system;

D'Angelo & De Zeeuw, 2009) or at a *macrolevel* (e.g., an approach to memory research; Matthies, 1982). Plasticity may refer either to *normal states* (e.g., the springtime reemergence of bird song; Lenn, 1992, or changes in oscillatory brain activity with musical training; Trainor, Shahin, & Roberts, 2009) or to *abnormal states* (e.g., changes in white matter tracts of aphasic patients undergoing intonation therapy; Schlaug, Marchina, & Norton, 2009). Plasticity may refer to a *belief* about the immature brain (e.g., that functional recovery will be greater in a younger organism; Webb et al. 1996) or to *evidence* that plasticity is a general property of the brain at any age (e.g., experience-dependent structural synaptic plasticity in the adult brain; Holtmaat & Svoboda, 2009). Plasticity is a reparative mechanism for the brain to adjust to lesions by remyelination, reorganization of circuits, and/or neural and behavioral compensation (Castellanos et al., 2010; Nudo et al., 1996, 2006; Leocani & Comi, 2006). Finally, in a longer, evolutionary time frame, plasticity refers to the development of culturally specific skills, like reading, in brain substrates originally used for other functions (Liberman, 1998; Sacks, 2010).

1. 2 The young age plasticity privilege and the "Kennard Principle'

Chronological age has long been linked to plasticity, such that greater plasticity is associated with a younger age and/or immaturity, an idea we term *the young age plasticity privilege*. This idea arose in part from misreading of Kennard's work in the 1930s and 1940s (see Dennis, 2010). Kennard had shown that age, but also factors other than age, predicted outcome after early brain lesions. Despite later support for Kennard's conclusions (e.g., Feldman, 2009; Giza & Prins, 2006; Goldman-Rakic, 1980; Pullela et al., 2006), the 'Kennard Principle' persists as a *belief* – even in the face of invented evidence (fictitious traumatic brain injury (TBI) case histories varying only in the age of the patient) - that children exhibit fewer problems and better recovery after brain insult than adolescents or adults (Hart & Faust, 1988; Webb et al., 1996).

2. Plasticity May Be Adaptive Or Maladaptive

Three questionable presuppositions continue to dominate discussions of plasticity. The first is that plasticity *is yoked to functional outcome*. The second is that plasticity *is functionally adaptive* (as evidenced by recent titles like "Harnessing neuroplasticity," Cramer et al., 2011). The third, an argument from design, is that plasticity *is designed to be adaptive*.

Almost 40 years ago, Schneider (1974; Schneider & Jhaveri, 1974) dissociated quantum of plasticity from functional outcome, finding that structural plasticity after lesions in the immature midbrain was more extensive than after lesions in the mature midbrain, but that function was poorer..

Although plasticity provides an evolutionary advantage in adapting to constantly changing internal and external environments, plastic mechanisms produce both adaptive and maladaptive change (Elbert & Heim, 2001 term the latter the 'dark side' of plasticity). Conditions such as musician's dystonia or writer's cramp occur because of neural plasticity in representational zones but involve dysfunction. Focal dystonia in musicians is associated with the same plastic brain changes that generate high levels of skilled performance (reorganization of the digits in the primary sensory area, Tamura et al., 2009). Therapy for focal dystonia involves returning the cortical finger representation to its original state (Candia et al., 2003). Immobilizing the dystonic hand in patients with writer's cramp produces a relative gray matter decrease in the contralateral primary motor hand area and a decrease in corticomotor excitability (Granert et al., 2011).

Plastic change is not *designed* to be adaptive or maladaptive, powerful or impotent. As Nava and Röder (2011) suggest, some forms of maladaptation may be like Gould's evolutionary

spandrels (Gould & Lewontin, 1979), a random side effect, not an intended direct result, of plasticity.

3. The Young Age Plasticity Privilege Has Been Overstated

Mental retardation has long been the elephant in the young age plasticity privilege room. Referring to the 'myth' of recovery from early brain damage, Isaacson noted,

> If the developing brain were completely "plastic" (a most unfortunate word) and any part capable of doing the work of any other, how are we to explain the tragedies of mental retardation resulting from biological problems occurring before birth? (Isaacson, 1975, p. 1)

Why are pervasive cognitive deficits more common after neurodevelopmental and early-acquired brain insults than after later childhood or adult lesions? How can disruptions of brain development generate plastic brain changes but the most widespread and life-long functional impairments? Why are the most profoundly debilitating and long-lasting cognitive-behavioral effects not associated with insults to the mature brain? In addition to the questions raised by mental retardation, the young age plasticity privilege has been challenged in a number of ways.

3.1 Epigenetic rescue in the adult brain

Epigenetics refers to heritable changes in gene function mediated by modifications to chromatin structure and covalent DNA modifications (methylation), but which do not involve permanent DNA alteration (Franklin & Mansuy, 2010; McGowan, Meaney, & Szyf, 2008). Epigenetic mechanisms program tissue specific patterns of gene expression; throughout life, epigenetics is like biochemical instructions written in pencil rather than indelible ink that can lead to dramatic changes in expression and/or function in response to environment and experience (Gosden & Feinberg, 2007). Epigenetic markers laid down in development dynamically regulate gene transcription in the adult brain (Miller & Sweatt, 2007).

Epigenetic restoration in adulthood may reverse neurological deficits. Rett syndrome, an X-linked neurodevelopmental disorder caused by mutations in the MeCP2 gene, is associated with aberrant synaptic function and behavior (Boggio et al., 2010; D'Cruz et al., 2010). Targeted reintroduction of functional MeCP2 rescues the behavioral abnormalities of MeCP2-deficient adult animals (Guy, Gan, Selfridge, Cobb, & Bird, 2007; Jugloff et al., 2008; Luikenhuis et al., 2004). In autism, a functionally impaired locus coeruleus-noradrenergic system may be transiently restored in the presence of fever (Mehler & Purpura, 2009). Treatment with a GABA receptor antagonist rescues cognitive function in adult mouse models of Down Syndrome (Fernandez et al., 2007). Pharmacological treatment in adult mice rescues the physiological and behavioral deficits of neurofibromatosis (Ehninger et al., 2008). While it has long been known that neurodevelopmental, neurodegenerative, and neuropsychiatric disorders are associated with aberrant epigenetic modifications (Gräff et al., 2011; Bartzokis, 2011), studies of epigenetic rescue in adulthood demonstrate the plasticity of epigenetic modification in the mature organism, although, to be sure, the mechanisms of action remain to be fully understood.

3.2 Adult neurogenesis

Neurogenesis, production of astrocytes, glia, and neural cells that connect and form pathways (Levitt, 2003), is largely completed during the pre-/perinatal period, but *adult* neurogenesis (Altman, 1962; see review in Kriegstein & Alvarez-Buylla, 2009) continues in the subgranular zone of the dentate gyrus and the subventricular zone of the lateral ventricle,

recapitulating stages of neural maturation during perinatal development, albeit at a slower pace (Overstreet-Wadiche et al., 2006). Adult neurogenesis promoes function; for example, neurogenesis in the adult forebrain is required for predator avoidance and sex-specific behaviors (Sakamoto et al., 2011). Neurogenesis increases after cerebral ischemia, epilepsy and bacterial meningitis, and decreases with chronic stress and aging. (Fields, 2005). Neonatal brain insults, such as repetitive seizures and hypoxia/ischemia, alter the integration, although not the production, of adult-generated dentate gyrus neurons (Pugh et al., 2011).

Neurons generated in adult life must form synapses with existing neurons and integrate with existing circuits (for review, see Imayoshi et al., 2011). The young age neurogenesis advantage rests not so much in the production of new neurons, as in integrating newly-formed neurons with existing networks without disturbing circuit function, a less complex problem in the immature brain.

3.3 Age-conserved plasticity mechanisms

Neural migration, survival, myelination, and synaptic function are subject to similar regulation throughout development. For example, master regulators of neural stem cells and neural development, such as the Notch signalling pathway, are expressed and active in the adult brain (Ables et al., 2011). Basic processes of myelination are disrupted in neurodevelopmental disorders (e.g., mutations in genes that control oligodendroglia or myelin development, such as Pelizaeus-Merzbacher disease, Fancy et al., 2011) and in birth pathologies (e.g., periventricular leukomalacia, Billiards et al., 2008). Regenerative remyelination shares mechanisms with primary myelination. Remyelination after white matter injury involves upregulation of several genes associated with the generation of oligodendrocytes during development. The recruitment phase of remyelination recapitulates aspects of primary myelination (e.g., platelet-derived growth factor is a mitogen in both development and remyelination; Fancy et al., 2011).

The development and regeneration of axons and dendrites share core mechanisms. Related processes may regulate Wallerian degeneration, degenerative forms of axon pruning in development, and models of axon degeneration in neurological disease (Low & Cheng, 2006). Mature CNS neurons regenerate injured axons by a molecular process apparently conserved across development; the limiting factor is neuronal competence to sustain long-distance regrowth by trophic factors and molecules in the extracellular matrix, a greater challenge in the adult brain.

3.4 Critical (but elastic) periods for development

Critical periods are time points in development when experiences strongly influence neurogenesis, brain sculpting, and learning (Hubel & Wiesel, 1963); for example, establishing ocular dominance columns in the visual cortex are established during early post-natal life (reviewed in Berardi et al., 2000). Critical periods are less precise in age timing and specificity than originally proposed (Johnson, 2005). Abnormal visual input can be disruptive even when it begins in adulthood (Daw, 1998; Lewis & Maurer, 2005). Practice improves visual acuity in adults with amblyopia (Levi, 2005). Age-at-cochlear implant variations in prelingually deaf children do not represent critical periods (Harrison et al., 2005). Real-time brain activation for artificial language learninng is similar in adults and children (Friederici, Steinhauer, & Pfeiger, 2002).

Multiple critical periods exist for different domains, different functions within a domain, and different time points. Visual deprivation in the monkey before 3 months of age affects scotopic sensitivity; deprivation before 6 months of age affects photopic spectral sensitivity;

and deprivation before 18–24 months affects spatial contrast sensitivity (although visual deprivation can affect binocularity even in adulthood, Harwerth et al., 1986).

Importantly, controllers other than age drive the onset and offset of critical periods (Michel & Tyler, 2005). Intracortical inhibition thresholds in visual cortex, not age, control onset and offset of the critical period, which can be reinstated in the mature brain by pharmacological or environmental manipulations (Spolidoro et al., 2009; Hensch, 2005; Sale et al., 2009).

3.5 Critical periods that minimize the effects of brain injury?

Are there critical periods when the brain can be injured with impunity, as Anderson et al. (2009) and Kolb et al. (2011) suggest? Early comparisons supporting this hypothesis confounded age at injury with differences in pathology, e.g. finding better recovery from aphasia in children with head injuries than in adults with arteritic strokes (e.g., Guttmann, 1942). In school age children and adults, recovery from aphasia induced by head trauma is better than that caused by vascular lesions – regardless of age at injury (e.g., Dennis, 1980b; Dennis, 2009). More recent papers continue to conflate age, pathology, and lesion laterality. Anderson et al. (2009) argued that children with brain injury in infancy have lower IQ scores than those injured in middle childhood, but the infancy group included 61% neoplasms and 9% trauma, whereas the middle childhood injury group had 32% neoplasms and 26% trauma. In the same data set, comparison of lesions before and after age 2 showed bilateral lesions to be significantly more frequent in the early group (analyses of Anderson et al., 2009, data by Lidzba et al., 2009). To demonstrate a critical period for immunity to brain damage, it would be necessary not only account for outcome-relevant variables other than age (pathology, etiology, laterality (or bilaterality) of lesions, seizures), but also to compare acquired disorders with the same pathology occurring at different ages. Because neuropathology itself is age-related, inferences about plasticity from comparisons across age are difficult and have frequently been over interpreted as demonstrating age-related plasticity.

3.6 “Recovery” and age at injury

The pathology confound is apparent in many animal and human studies that report better functional outcomes and recovery after an earlier age at injury. For example, early studies asserted that children with left-sided brain injury rarely showed adult aphasic syndromes (e.g., Basser, 1962; Lenneberg, 1967). Later studies challenged the proposal that language recovery is better with early lesions (e.g., Dennis 1980; Dennis, 2009; Dennis & Whitaker, 1977).

While one type of cortical-spinal reorganization (strengthening of fast-conducting ipsilateral projections) is better with a younger age at injury (reviewed in Staudt, 2010), there is no overall advantage to earlier rather than later brain injury in children. Especially when higher cortical functions are considered, outcome also depends on pathology, how outcome is measured, and time since injury.

Age at injury effects vary within pathology, a better test of age-related plasticity hypotheses. Children treated for malignant posterior fossa medulloblastomas have poorer outcomes with a younger age at diagnosis and treatment (Dennis et al., 1996). With active, ongoing pathological processes such as seizures, in contrast, an early age at treatment may be functionally positive. For example, children with congenital Sturge-Weber syndrome have better outcomes with earlier surgery and seizure control (Hoffman et al., 1979). Differences between (rather than within) pathologies may be less salient when seizures drive aberrant function (Kadis et al., 2009).

Plastic reorganization after early-onset brain lesions may produce considerable but incomplete functionality. After early-onset pre- and perinatal lesions, controlling both paretic and non-paretic hand with the contralesional hemisphere, while advantageous, comes with a cost that adult-onset lesions does not bear - involuntary synkinesias or mirror movements (Müller et al., 1997). After left hemisphere surgery for early-onset seizures, language is functional but syntactically limited (Dennis & Kohn, 1975; Dennis & Whitaker, 1976; Kohn, 1980). While IQ scores are generally within normal limits after childhood TBI, social-cognitive and social-affective functions are impaired (Dennis et al., 2013).

Age at injury effects must be considered in the context of time since injury. After childhood-acquired aphasia, better language function is associated with activation of left anterior language regions over time (Elkana et al., 2011). Time since injury effects operate differently after childhood- and adult-onset injuries. After TBI, decrease in cerebral blood flow is similar in juvenile and adult mice and both lose ipsilateral cortical volumes, but in different time frames (Claus et al., 2010).

Diverse outcome patterns over time since injury have been identified for children with brain disorders. The *recovery pattern* involves deficits maximal soon after the injury but abating thereafter (recovery pattern). For childhood-acquired injuries, some age-at-injury effects are more pronounced and behavioral effects are more volatile in the period soon after the injury (e.g., Wu et al., 2010). The response inhibition deficit in ADHD following childhood TBI is most pronounced soon after the injury but recovers with increasing time since injury (Schachar et al., 2004). The *growing into a deficit* (Kennard, 1944) pattern is characterized by mild deficits soon after the injury that increase with time. Children with preschool mild TBI grow into deficits, exhibiting increasing cognitive-behavioral deficits over 7–13 years of age (McKinlay et al., 2010). The *arrested development* pattern involves deficits that improve but fail to advance to developmentally appropriate levels. Compared to his co-twin, a child with an arterial stroke in the language areas of the left hemisphere at age 6 developed immediate, severe syntactic deficits that improved over some years to their level at the time of the stroke, but failed to develop thereafter (Hetherington & Dennis, 2004). After cerebellar tumor removal in children, behavioral improvements continue beyond 3 months, but are developmentally incomplete at one year post-injury (Küper et al., 2013).

3.7 Evidence for greater impairment with a younger age at injury

Comparisons of outcomes within pathologies in individuals varying in age show greater morbidity in children vs. adults, and in younger vs. older children. A younger age at diagnosis and radiation treatment in children with primitive neuroectoermal cerebellar tumors is associated with poorer outcome (Hoppe-Hirsch et al., 1990; Radcliffe et al., 1994). A form of acquired aphasia, mutism with subsequent dysarthria in which previously acquired language skills are lost (DiCataldo et al., 2001; Dailey et al., 1995; Doxey et al., 1999; Huber-Okrainec et al., 2001; Humphreys, 1989; Rekate et al., 1985; Van Dongen et al., 1994; Van Mourik et al., 1998) has been identified in children, but not in adults, after surgery for posterior fossa tumors. While both childhood and adult cerebellar lesions produce a “cerebellar cognitive affective syndrome” (Schmahmann, 2010), adult cerebellar damage generally results in milder and/or more transient cognitive difficulties (Alexander et al., 2012). Compared to children with an older age at TBI, children with TBI in infancy and toddlerhood have more severe and persisting sequelae and more protracted recovery (Ewing-Cobbs et al., 2006; Koskiniemi et al., 1995).

3.8 Experiential plasticity over the lifespan

Over the lifespan, brain and behavior change in response to use, disuse, training, and enrichment (Angelucci et al., 2009; Chaddock et al., 2011; Cotman & Berchtold, 2002;

Jaeggi et al., 2011; Klingberg, 2010). Early environments, maternal behavior and diet shape gene expression, tissue function and disease risk throughout life (Caldji et al., 1998; McGowan, Meaney, & Szyf, 2008; Sandovici et al., 2011). Training changes the adult brain (e.g., adult second language proficiency changes language-related brain regions, Hernandez & Li, 2007; Stein et al., 2012). Even experience-dependent plasticity of white matter microstructure (e.g., Mackey, Whitaker, & Bunge, 2012) is similar in younger and older adults (Lövdén et al., 2010).

Experiential plasticity operates in individuals with brain compromise at any age. Musical training enhances function in individuals with Williams Syndrome (Martens et al., 2011). Enriched environments compensate for the effects of acquired cerebellar damage (Cutuli et al., 2011; Foti et al., 2011) and traumatic brain injury (Kolb et al., 2011; Kovesdi et al., 2011). Even with degenerative brain damage, exposure to an enriched environment may sustain cognitive function (Green & Bavelier, 2008) and be associated with a slower rate of decline.

4. Plastic Change Operates In Concert With Homeostatic Mechanisms Regulating Change

Unbridled plasticity would generate an infinitely malleable, novelty-adaptive, and lesion-resilient brain that, at the same time, would be slow to learn and unable to automatize learning (or fast to learn but poor to retain). Unbridled stable homeostasis would generate a brain that could respond quickly to existing routines and information, but respond poorly to novelty or insult. Whether plasticity will be adaptive or maladaptive depends on homeostatic regulation, which exists at the level of gene, transcript, protein, metabolite, cell, and brain (Broderick & Craddock, 2012).

Traditional forms of synaptic plasticity (long-term potentiation or depression) occur in the context of stabilizing forces that provide homeostatic stability to neurons and networks. At the cellular level, excitation operates within an optimal range around a set point, beyond which excitation is adjusted by scaling up or down to maintain an appropriate level of function. At the network level, homeostasis stabilizes learning and changing connectivity via synaptic scaling, which adjusts the gain of the input and modifies the excitation-inhibition balance, and mechanisms that target intrinsic neuronal excitability, which modify contribution of a neuron to circuit function without changing synaptic currents (Pozo & Goda, 2010; Turrigiano & Nelson, 2004; Turrigiano, 2011). At the neuronal level, homeostasis balances excitation and inhibition in the face of morphological change or protein turnover, preventing activity-dependent plasticity from driving neural activity to excess excitation or quiescence (Marder & Prinz, 2002). The formation of connections governed by neurons driven to reach homeostasis can account for critical connectivity in developmental neural networks (Tetzlaff et al., 2010). Whereas synaptic plasticity and learning are achieved by positive feedback, homeostasis generally involves negative feedback.

5. Mechanisms of Plastic Developmental Change Expose The Immature Organism To Adverse Events

Brain development involves a complex sequence of plastic changes occurring over a protracted time span (Fields, 2005; Yakovlev & Lecours, 1967), and occurs in the context of age-dependent variations in metabolic rate, blood flow, neurotransmitter activity, and ability to tolerate oxidative stress (Morrison, Fraser, & Cepinskas, 2012). The same developmental mechanisms that promote plastic change may expose the organism to adverse outcomes.

Insult to an immature brain alters not only currently active brain development, including myelination, axon and dendrite growth, synaptogenesis, and proliferation of microglia and astrocytes (Rees et al., 2011), but also future brain development, involving myelination and cortical thinning (Ewing-Cobbs et al., 2008; Wilde, Hunter, & Bigler, 2012), and even neurodegeneration (Wu et al., 2010). A focus on plasticity as the mechanism for responding to environmental manipulations and recovery from brain injury has downplayed how dynamic change elevates the risk for a range of physiological and functional perturbations.

Newly formed neurons, the products of plasticity, have a low threshold for disturbance. The peak of human subplate neuron development in premature infants is coincident with the gestational ages of greatest vulnerability to perinatal brain injury (McQuillen & Ferriero, 2005). Compared to mature neurons, newly-formed dentate gyrus neurons in the adult brain exhibit increased neural plasticity, revealed by enhanced long-term potentiation (Schmidt-Hieber et al., 2004). However, although enhanced ability for long-term potentiation facilitates learning, neurons forming synapses have a low perturbation threshold (Kelsch, Sim, & Lois, 2010; Deisseroth et al., 2004; Schmidt-Hieber et al., 2004).

Three interconnected processes – oxidative stress, microglia phagocytosis, and neuroinflammation – have both beneficial and harmful effects. These processes are operative throughout the lifespan and are activated by brain injury, so open the immature and aging organisms, particularly, to both negative and positive effects. Developing neurons are susceptible to excitotoxicity, oxidative stress, and to inflammation (Morrison, Fraser, & Cepinskas, 2012).

Oxidative stress is caused by the imbalance between generation and detoxification of reactive oxygen and nitrogen species (Wang & Michaelis, 2010), and select neuron populations are vulnerable to oxidative stress, including those in the hippocampus and cerebellar granule cell layer (Wang et al, 2007). While reactive oxygen and nitrogen species are harmful, they have a beneficial, signaling, function that neurons use to responds to environmental cues (Gutierrez et al., 2006). Phagocytosis by microglia has a beneficial effect on development because microglia eat apoptotic cells during development and in adult neurogenesis, promoting brain modeling; but phagocytosis can also kill normal cells during inflammation (Sierra, Abiega, Shahraz, & Neumann, 2013).

Neuroinflammation is a common response to trauma, has beneficial effects on injured brain parenchyma and neuronal survival, and may pave the way for reparative processes. On the other hand, it also generates adverse effects including cell death, which contribute to secondary brain damage and neurological dysfunction (Lenzlinger, Morganti-Kossmann, Laurer, & McIntosh, 2001; Morganti-Kossmann et al., 2002). Neuroinflammation is related to changes in the brain following traumatic brain injury (TBI), including suppressed neurogenesis (Acosta et al., 2013) and chronic white matter alterations (Johnson et al., 2013). Individual differences in chronic neuroinflammatory change associated with TBI may account for variability in delayed effects in TBI survivors, such as post-traumatic epilepsy and the onset of neuropsychiatric disorders (Bigler, 2012).

Some metabolic effects of TBI may be especially disruptive in the immature organism. Increased anisotropic diffusion produces cytotoxic edema after TBI, and the magnitude and duration of these abnormalities appear to be greater in pediatric patients (Mayer et al., 2012). Apoptotic neurodegeneration following trauma is markedly enhanced in the immature brain (Bittigau, Sifringer, Pohl et al. 1999). Mechanisms that facilitate developmental plasticity may exacerbate damage resulting from by brain injury during development.

6. Many Childhood Disorders Involve Plasticity-Homeostasis Disequilibrium

Do maladaptive outcomes arise from disequilibrium of plasticity and homeostasis? Certainly, synaptic plasticity-homeostasis equilibrium is disrupted in several pediatric neurological disorders (Johnston, 2009; Johnston et al., 2009). The SynGAP protein may act as a developmental repressor of neural excitability and promote dendritic spine synapse maturation and behavior; pathogenic SynGAP1 mutations prompt early maturation and enhanced excitation of hippocampal spine synapses and behavioral abnormalities (Clement et al., 2012). Chondroitin sulphate proteoglycans in extracellular matrix of the adult brain restrict plasticity and their digestion reactivates it. Animals lacking cartilage link protein (upregulated in visual cortex as perineuronal nets form during development and after dark rearing) have attenuated perineuronal nets and persistent plasticity (Carulli et al., 2010). Both attenuated and persisting plasticity are forms of homeostatic dysequilibrium.

6.1 Epilepsy as a disorder of neuron circuit homeostasis

Epilepsy is a neuronal circuit excitability disorder characterized by spontaneous recurrent seizures. A balance of excitatory (glutamate) and inhibitory (GABA) neurotransmission controls excitability of neuronal circuits and homeostasis is important for epileptogenesis, a process involving complex disruption of self-regulatory mechanisms (Boison, Sandau, Ruskin, Kawamura, & Masino, 2013) arising from insufficient or excessive compensatory mechanisms in response to a change in network activity (Fritschy, 2008; Transande & Ramirez, 2007)..

Balancing homeostasis and plasticity involves myriad presynaptic, postsynaptic, ion channel, and extracellular matrix signaling mechanisms (Turrigiano, 2011; Pozo & Goda, 2010; Transande & Ramirez, 2007; Dityatev, 2010). A complex cascade of events leads to the evolution of epilepsy; for example, the spatial pattern of trauma (whether compact or diffuse) affects the propensity for developing posttraumatic epileptic activity (Volman, Bazhenov, & Sejnowski, 2011).

In post-traumatic epilepsy emergent after a latent period after TBI, trauma produces damaged neurons and physical undercutting of neuronal circuits; this causes deafferentation and neuronal injury and fewer neurons in the circuits. As homeostatic mechanisms attempt to re-establish the baseline level of excitation, the network becomes synaptically reorganized and hyperexcitable, producing post-traumatic seizures (Timofeev, Bazhenov, Avramescu, & Nita, 2010; Avramescu & Timofeev, 2008). Post-traumatic generation of paroxysmal events does not require structural changes in connectivity, and trauma-induced change in functional rather than anatomical connectivity might be sufficient for the evolution of epilepsy (Volman, Sejnowski, & Bashenov, 2011). Homeostatic plasticity following TBI may contribute to both adaptive functional recovery and in maladaptive epileptogenesis occurring between an initial cortical insult and an explicit onset of late epilepsy (Prince et al., 2009; Timofeev et al., 2010). The challenge in targeted treatments of TBI is to prevent epileptogenesis and post-traumatic epilepsy with pharmacological interventions without compromising adaptive function (Prince et al., 2009).

6.2 Dysregulated neurogenesis

Some neurodevelopmental disorders feature plastic but dysregulated neurogenesis. In DiGeorge syndrome, the 22q11.2 deletion results in diminished gene dosage, reduced cortical neurogenesis, and disrupted interneuron migration (Meechan et al., 2009), including clinical manifestation of autism (Wegiel, Kuchna et al. 2010). Disturbances of cortical development produce abnormalities of cortical migration, including lissencephaly (reduction

in cerebral folding), cortical dysplasia (disorganization of cortical lamination), heterotopia (malposition of cortical gray matter in white matter fiber tracts), and polymicrogyria (excessive folding of cortical surface) (Golden & Harding, 2010).

6.3. Underpruning and overpruning

Pruning of developing synapses and dendritic spines during CNS development (Buss, Sun, & Oppenheim, 2006; Huttenlocher, 1979; Paolicelli et al., 2011; Saxena & Caroni, 2007; Vanderhaeghen & Cheng, 2010) regulates brain size and shape (Haydar, Kuan et al. 1999). Apoptosis continues into the third decade of life (Casey, Giedd et al., 2000; Giorgio, Watkins et al., 2010; O'Donnell et al., 2005; Paus, Keshavan, & Geidd, 2008; Petanjek et al., 2011).

Synaptic and dendrite instability has been implicated in neurodevelopmental disorders (Jan & Jan, 2010; Parrish et al., 2006). Autism (Pardo & Eberhart, 2007; Kelleher & Bear, 2008), fragile X syndrome (Bagni & Greenough, 2005); and Rett syndrome (Ramocki & Zoghbi, 2008) are associated with synaptic *underpruning*, resulting in enlarged regional brain size, due to overgrowth or lack of dendrite pruning and modification in neuron number.

Disorders with later onset show synaptic *overpruning* or failed maintenance of dendrites. Schizophrenia is associated with loss of dendritic spines on cerebral neocortical pyramidal neurons, decreased density of glutaminergic neurons, and microgliosis (Garey, 2010; Glantz & Lewis, 2000). Progressive gray matter loss occurs concomitant with the development of late adolescence schizophrenia, suggesting synaptic overpruning (Garey et al., 1998; Steen et al., 2005). Overexpression or underexpression of genetic variation or mutations in factors such as DISC-1, whose protein binding is regulated by activation of the NMDA-type glutamate receptor, have been implicated in the loss of synaptic function in schizophrenia (Hayashi-Takagi, Barker, & Sawa, 2011). Dysbindin, a gene linked to schizophrenia, is involved in the homeostatic modulation of neurotransmission (Dickman & Davis, 2009).

Acquired childhood lesions disrupt normal apoptosis. Cortical thinning after TBI in several brain regions overlaps with reduced gray matter that occurs with normal pruning, so areas destined for reduction as part of the normal pruning/programmed cell death get extra reduction (Merkley et al., 2008). Loss of cortical thickness and connectivity in more severe TBI (Bigler et al., 2010; Bigler, Abildskov et al., 2010) may disrupt developmentally programmed pruning (Bigler, Abildskov et al., 2010; Bendlin, Ries et al., 2008; Levine, Kovacevic et al., 2008; Wilde, Hunter et al., 2005; Wilde, Hunter, & Bigler, 2012).

6.4 Too-fat and too-thin brains

Neurodevelopmental disorders produce both overgrowth and undergrowth of cortical volume, cortical thickness, and cortical complexity. The homeostatic failure to regulate plastic growth in the cerebral cortex is associated with dysfunction.

Reduced total or regional cortical volume has been reported in 22q11.2 deletion syndrome (Eliez et al. 2000), Angelman syndrome (Tan et al. 2011), Down syndrome (Weis et al. 1991), Fragile X syndrome (Kates et al. 2002), Rett syndrome (Subramaniam et al.1997), and Cohen syndrome (Kivitie-Kallio et al. 1998).. Excess superior and middle temporal lobe volume in Turner syndrome is associated with poor language (Rae et al. 2004). Congenital amusia is associated with extra volume in the right inferior frontal gyrus and auditory cortex (Hyde et al. 2007). More radiate white matter in the primary motor cortex is associated with motor impairment in autism (Mostofsky et al. 2007).

Cortical volume reflects both cortical thickness and cortical gyrification (the process by which the cortical surface folds to create gyral and sulcal regions), both of which change

over normal development (e.g., Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995; Giedd et al. 1999; Giedd 2004; Gogtay et al. 2004; Mangin et al. 2010; Magnotta et al. 1999; Sowell et al. 2003; Shaw et al. 2008; Raznahan et al. 2011; White et al. 2010), and are aberrant in neurodevelopmental disorders. Regions of thicker cortex have been reported in fetal alcohol spectrum disorder (Sowell et al. 2008) and Williams syndrome (Thompson et al. 2005); regions of thinner cortex in adolescents born preterm (Nagy et al. 2011), ADHD (Makris et al. 2007; Narr et al. 2009; Batty et al. 2010), childhood- and adolescent-onset schizophrenia (White et al. 2003), and temporal lobe epilepsy (Lin et al. 2007; Mueller et al. 2009). Thicker and thinner cortical regions co-exist in 22q11.2 deletion syndrome (Bearden et al. 2007, 2009; Schaer et al. 2009), autism spectrum disorder (Hyde et al. 2010; Jiao et al. 2010), and Turner syndrome (Raznahan et al. 2010). Regions of higher gyrification have been reported in 22q11.2 deletion syndrome (Bearden et al. 2009), autism spectrum disorder (Awate et al. 2008), children born preterm (Kesler et al. 2006), and Williams syndrome (Thompson et al. 2005; Gaser et al. 2006); regions of lower gyrification in ADHD (Wolosin et al. 2009), dyslexia (Casanova et al. 2004), intellectual disability (Zhang et al. 2010), obsessive-compulsive disorder (Wobrock et al. 2010), and Turner syndrome (Raznahan et al. 2010). Regions of both higher and lower gyrification have been reported in schizophrenia (White and Hilgetag 2011), and temporal lobe epilepsy (Lin et al. 2007; Voets et al. 2011).

Individuals with spina bifida myelomeningocele exhibit bidirectional anomalies of cortical thickness and cortical gyrification (Juranek et al. 2008; Juranek & Salman 2010 (Fig. 1). Treble et al (2012) investigated the functional effects of these failures of homeostatic regulation of cortical development. They found a negative association between cortical thickness and gyrification, such that aberrant plasticity in one feature was correlated with compensatory homeostasis in the second feature. For example, excessive gyrification in the inferior parietal and supramarginal cortices resulted in an aberrantly thin cortex that folded more compactly. More deviant levels of cortical thickness and gyrification—whether higher or lower relative to the typically developing comparison group—were associated with impaired function.

Cerebellar resculpting in spina bifida meningomyelocele, on the other hand, may promote increased functionality of eye movements. The small posterior fossa in this condition is caused by cerebrospinal fluid leak through the spinal defect that prevents distension of the embryonic ventricular system (McLone & Knepper, 1989), which prevents expansion of the posterior fossa and reconfigures the cerebellum (Juranek et al., 2010). Hyperdevelopment of the midsagittal vermis in spina bifida meningomyelocele is associated with sparing of ocular motor function (Salman, Dennis, & Sharpe, 2009).

6.5 Unbalanced global and local circuit connectivity

Over development, brain circuits become established as a series of hubs and connectors (van den Heuvel & Sporns, 2011) promoting both local and remote connectivity (Vogel et al., 2010). Hubs within a brain network tend to be more densely connected among themselves than with nodes of a lower degree, a Rich-Club organization (Colizza et al., 2006) that confers a level of resilience and plasticity not available to functionally specialized networks lacking such structure.

Circuitry is important in considering age and plasticity. Functional connectivity of the same brain region is different in children and adults (e.g., Ezekiel, Bosma, & Morton, 2013), so it is not surprising that connectivity develops abnormally in a number of neurodevelopmental disorders or that Rich-Club organization may be important for long-distance brain connectivity (van der Heuvel et al., 2009) in these conditions.

Individuals with autism show evidence of both local over-connectivity and long-distance under-connectivity (e.g., Belmonte et al., 2004; Casanova & Trippe, 2009), with more severe disruptions in later-developing cortical regions (Wass, 2011), and weak long-range inhibitory connections (JS Anderson et al., 2011). This aberrant connectivity has functional consequences. Short-range dynamic connectivity increases and long-range dynamic connectivity decreases with increasing autism severity (Barttfield et al., 2011). Individuals with autism use atypical brain regions to perform tasks (Di Martino et al., 2009). Behavioral markers of autism (impaired language, lack of social reciprocity, repetitive behavior) may involve disordered communication between frontal and posterior brain regions (Just et al., 2007; Schipul, Keller & Just, 2011).

Experience changes brain circuits in both typically developing children and special populations (Gabrieli, 2009; Hoeft et al., 2011; Perfetti et al., 2007; Rezaie et al., 2011). Reading intervention in children with dyslexia shifts neural activity from a more bilateral pattern reflecting underactivation of the left middle temporal and/or lateral occipital regions to more lateralized pattern involving greater left temporo-occipital cortical activity (Simos et al., 2002; Shaywitz et al., 2004; Spironelli et al. 2010).

6.6 Heterosynchrony

Dysregulation of homeostatic processes may create a heterosynchrony, a mismatch between two processes that are normally linked in time whereby accelerating or decelerating of one or both shifts their relative standing at various points in development. Heterosynchrony may help explain why some functional impairments after childhood brain disorders, rather than abating with age and development, become increasingly apparent over time.

Rats exposed to valproate, a neuronal maturational promoter, exhibit hyper-connectivity in cortical circuits. Postnatal rat pups treated with valproate show premature adult-like intrinsic electrophysiological properties in 40% of the temporal association cortex, cortical hypertrophy, and reduced social play, suggesting an association of behavioral dysfunction with accelerated timing of cortical maturation (Chomiak et al., 2010).

Spina bifida meningomyelocele involves attenuation of long association pathways including the corticopontocerebellar tract, frontostriatal and thalamofrontal tracts, limbic and commissural tracts, and association and projection pathways (Fletcher et al. 2005; Hasan, Eluvathingal et al. 2008a; Hasan, Sankar et al. 2008b; Juranek & Salman, 2010; Vachha et al. 2006). Over ages 8–16 years, more efficient myelination of the inferior longitudinal fasciculus (connecting the occipital and temporal lobes) is reflected in a decrease in radial diffusion on DTI. Children with spina bifida meningomyelocele, however, show no change, or even increased diffusivity in this tract, indicating poorer myelination and even early degenerative processes over age (Hasan et al., 2008). An asynchronous relation between myelination and age means that a key segment of childhood development lacks white matter functionality.

The timing of sleep relative to the 24-hour day changes across the lifespan, with progressively later sleep-wake times during childhood and adolescence (Carskadon et al., 1993), and earlier times in aging adults (Carrier et al., 1997). Edelstein et al., 2012 measured *sleep chronotype* (Roenneberg et al., 2003; Roenneberg, 2007) in 7–55 year old individuals with spina bifida meningomyelocele, finding the typical relationship between chronotype and age, even though the phase relationship between sleep-wake timing and 24 hour day in controls trended downward at the age when it peaked in spina bifida meningomyelocele (Edelstein et al., 2012). Aberrant synchronization of circadian rhythms to the 24-hour day may contribute to sleep problems in this and in other neurodevelopmental disorders (Glickman, 2010; Harvey & Kennedy, 2002).

Wu et al. (2010) found heterosynchronous processes over time since injury in an adolescent with TBI. Microstructure regrowth (evidenced by increased fractional anisotropy and fiber density) was accompanied by accelerated degenerative volume loss at an earlier-than-normal point in the lifespan.

6.7 Synaptic plasticity and learning

The model for learning has been activity-dependent adaptation, *Hebbian plasticity*, a positive feedback mechanism that includes long-term potentiation and long term depression (Feldman, 2009). Positive feedback mechanisms must be balanced by compensatory and homeostatic negative feedback and prediction mechanisms.

Neurons change the strength of their synapses and connections in response to extrinsic stimuli. Hebbian synaptic changes are associative, rapid and input specific (Pozo & Goda, 2010); because repeatedly and persistently co-active cells increase connective strength among populations of interconnected neurons, they reinforce synapses that are co-activated with certain experiences, thereby providing a putative cellular basis for learning and memory (Neves et al., 2008). Cortical networks undergo adaptations during learning including specific increases in dendritic complexity and spines. Structural elaborations during learning involve discrete subsets of cells preferentially activated by experience (Wang et al., 2011).

Novel stimuli become predictable after association with other neural signals, so the brain needs to distinguish predictable and novel signals. Learning is facilitated by the homeostatic mechanisms of *anti-Hebbian plasticity*, a form of learning involving reducing synaptic strength between neurons after one neuron produces an action potential in another, and which provides the basis for novelty detection (Roberts & Leen, 2010). Spike-timing-dependent plasticity, which modifies the strength of connections between neurons based on the relative timing of a particular neuron's output and input spikes, is also important (Markram et al., 2011). Spike-timing-dependent synaptic plasticity at a synapse carrying predictive signals sculpts a negative image of predictable sensory patterns from background sensorimotor activity.

6.8 Behavioral homeostasis

At the level of behavior, across groups and within individuals, homeostasis involves adjusting behavior to maintain a target level of response to environmental cues or triggers A range of behavioral dysfunction in neurodevelopmental and childhood acquired brain disorders is associated with dysregulation of behavior around a homeostatic baseline.

Attention, normally maintained within a target range, may be dysregulated and subject to performance extremes. Russell et al. (2006) propose that ADHD increases trial-by-trial performance variability (Scaglione et al., 2011) because of inefficient astrocyte function from deficient ATP production in neurons, over milliseconds, and deficient developmental myelination of axons. Inhibition of return is a form of automatic attention and is indexed by a longer time to return to a previously attended cue location compared to a novel location (Klein, 2000). Children with spina bifida meningomyelocele and beaking of the midbrain tectum exhibit attenuated inhibition of return (Dennis et al., 2005), showing dysregulation of automatic attention. When bisecting horizontal and vertical lines, these children exhibit an enhanced Weber fraction, a larger zone of subjective variability (Dennis et al., 2005).

Acquired deafness results in a sensory deprived cortical region with decreased inhibitory synaptic transmission. Hearing-lesioned animals exhibit tinnitus with a pitch in the hearing loss range, and drugs that enhances inhibition (but not those that reduce excitation) eliminate

tinnitus, suggesting that sensory-induced homeostatic down-regulation of inhibitory synapses generates tinnitus (Yang et al., 2011).

Restoring cellular homeostasis may rescue behavior in mouse models of complex behavioral disorders. Increased cellular inhibition moderately ameliorates social deficits in mice experimentally subjected to elevation of cellular excitation-inhibition balance (Yizhar et al., 2011).

The symptom spectrum in children and adults with acquired cerebellar lesions has been proposed to reflect exaggeration (overshoot, dysmetria) and/or diminution (hypotonia, hypometria), (Schmahmann, 2010). The immature and adult cerebellum may modulate the speed, capacity, consistency, and appropriateness of cognitive processes, maintaining them around a homeostatic, context-appropriate baseline (Schmahmann, 2010).

7. Discussion

This review has considered major challenges to the idea of a global young age plasticity privilege: Plasticity itself is neutral and ‘intends’ no particular outcome, which may be either adaptive or maladaptive; many plasticity mechanisms are not intrinsically tied to age; homeostatic mechanisms regulate plastic change at any age; and the outcome of many neurodevelopmental disorders and childhood acquired brain insults is related to disequilibrium of plasticity and homeostasis. Plasticity in any neural or behavioral system is not unbridled, and homeostatic processes that limit change counter plastic processes that promote change at the level of brain and behavior. Plasticity – related to change – and homeostasis –related to stability – are properties of brain and behavior at every point in the lifespan. To the extent that plasticity is an intrinsic property of the brain, it exists in a normal young brain, a normal older brain, and in brains of any age compromised by congenital malformations or acquired insult. Whether the outcome of plasticity is adaptive or maladaptive depends on the equilibrium between plastic and homeostatic processes.

Is there a basis for the continuing belief in the young age plasticity principle? The answer depends on how the question is posed. It is hardly news that damage to the young brain has functional consequences (Cotard, 1868), that some differences in the effects of brain injury are related to age at injury, or that particular outcomes may be more favorable with an earlier age at injury (Staudt, 2010). Whether an early age at injury provides a general adaptive advantage depends on when and how outcome is assessed, and even adaptive outcomes often come with symptoms or developmental truncation not observed with later age at injury.

Age is one factor in *describing* the outcomes of neurodevelopmental disorders or acquired brain lesions (Dennis, 2000, Taylor & Alden, 1997), but is not a mechanism to *explain* plasticity. Age marks programmed events that are malleable over the lifespan but that typically occur at a particular age point. Age-based plasticity has sometimes been assumed rather than proven; age may be a proxy for more fundamental processes, such as those in the epigenome, that are the causal factor in outcome; and age is correlated with differences in pathology. The age span for neural plasticity can be shrunk or expanded by manipulations of gene expression or by experience. Mutable function is tied not to age but to key developmental processes; for example, intracortical inhibition thresholds – not age- control critical periods for monocular vision. A focus on age an explanation distracts from the discovery of these mechanisms (e.g., how endogenous and self-terminating learning processes control the duration of critical periods; Johnson, 2005).

If the age issue is conceived as a contest between early plasticity and later specialization, then the answer is *no*, there is little basis for a continuing belief in the young age plasticity

privilege. Plasticity vs. specialization is simply a variation of the nature-nurture debate, a false dichotomy (Traynor & Singleton, 2010) since a functional brain must be both adaptable and specialized. If, on the other hand, the age question concerns identifying brain regions and cell populations with age-related reactions to excitotoxicity, oxidative stress, and inflammation (e.g., Ferriero & Miller, 2010), then the answer is *yes* because it prompts the search for both adaptive processes like neural repair and maladaptive processes like accelerated apoptosis and degeneration.

Age is also a marker for environmental problems that plastic neural and behavioral processes have to solve, which alter as the environment changes (Nava & Röder, 2011), within and between points in development. Brain and behavioral development occurs within a highly constrained, genetically organized but changing environment that has bidirectional effects on the brain; at each point in development, the child has a stable state and a plasticity history that limit which factors will influence its further development (Stiles & Jernigan, 2010). By typicality, enrichment, or deprivation, the environment affords experiences that iteratively shape brain development (Greenough et al., 1987).

Age-conserved and age-related plastic processes and homeostatic mechanisms provide flexibility in negotiating changing environmental challenges to meet life demands (Deisseroth et al., 2004; Kelsch, Sim & Lois, 2010). As internal and external environments change over age and development, a combination of plastic and homeostatic mechanisms solve emerging neural and behavioral problems. The tango between short-lived plasticity and longer-term robust specialization, on the one hand, and homeostatic forces, on the other, enables the immature brain to shape and reshape itself with experience, use, and disuse; adopt new stable phenotypes; and reengage, reorganize and compensate to restore old phenotypes shattered by brain insult.

But the outcome of the dance may be maladaptive as well as adaptive. The same mechanisms that propel developmental change expose the immature brain to adverse events. In attempting to understand age, plasticity, and homeostasis, the traditional, roseate view of a universal young age plasticity privilege needs to be tempered with an awareness of the huge challenge facing an immature brain: maintaining equilibrium between change and stability when the arc of both is in a state of constant jitter and when novel environmental demands emerge constantly.

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Highlights

- Plasticity is neutral with respect to outcome. Although the effects of plasticity are often beneficial, the outcome of plasticity may be adaptive or maladaptive.
- The young age plasticity privilege has been overstated.
- Plastic change operates in concert with homeostatic mechanisms regulating change at every point in the lifespan.
- The same mechanisms that propel developmental change expose the immature brain to adverse events, making it more difficult for the immature than for the mature brain to sustain equilibrium between plasticity and homeostasis.
- Poor outcome in many neurodevelopmental disorders and childhood acquired brain insults is related to disequilibrium between plasticity and homeostasis.

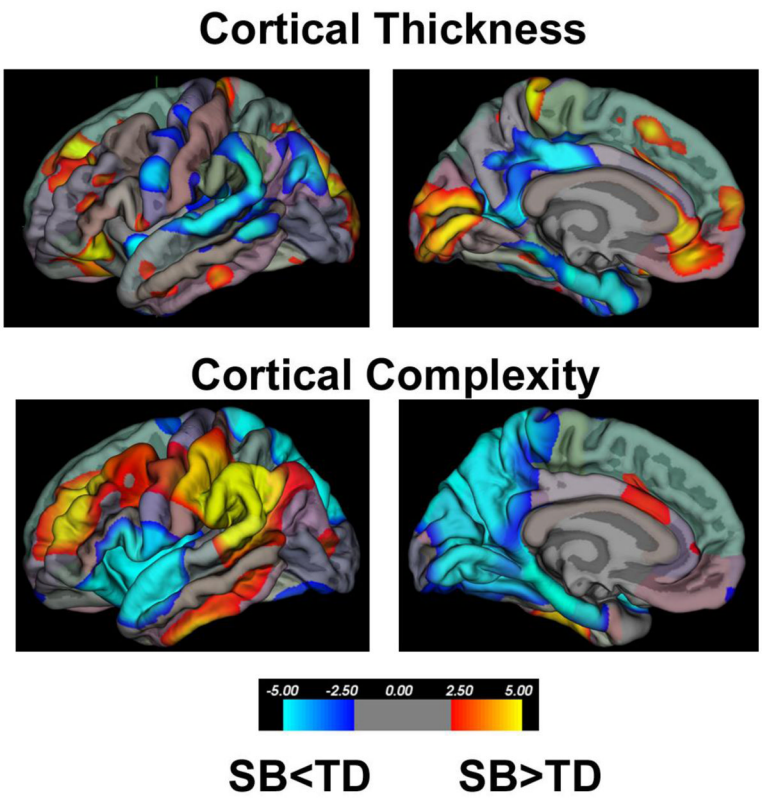

Figure 1.
Spatial representation of significant group differences (spina bifida myelomeningocele relative to typically developing controls) in surface-based analyses of cortical thickness (top row) and cortical complexity (bottom row). Whereas some frontal regions have increased cortical thickness and increased cortical complexity in spina bifida myelomeningocele relative to typically developing (e.g. superior frontal and middle frontal gyri), temporal and posterior areas exhibit decreased cortical thickness and decreased cortical complexity (e.g. isthmus of the cingulate, parahippocampal, and precuneus regions). (adapted from Treble et al.,2012, Juranek & Salman, 2010).