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Review

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 as follows:

- 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.

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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 the 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 as follows:

- 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 and 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 and 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 and 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 et al., 2009) or to *abnormal states* (e.g., changes in white matter tracts of aphasic patients undergoing intonation therapy; Schlaug et al., 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 and 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; Nudo, 2006; Leocani and 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 and 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 and 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*

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