13

Plasticity beyond Early Development

Hypotheses and Questions

Ulman Lindenberger

Abstract

Applying insights from research on critical periods in early development, this chapter outlines a life-span research agenda on human plasticity and uses it as the conceptual foundation for a set of research hypotheses and open questions. *Plasticity* is defined as the capacity for lasting changes in brain structure associated with expansions in behavioral repertoire. As a complement to plasticity, *flexibility* refers to the instantiation and reconfiguration of the existing behavioral repertoire during periods of stability that are characterized by the absence of structural change. Mammalian and avian brains evolve through cycles of plasticity and stability, with a general trend toward stability. Animal work on critical periods in motor and sensory development substantiates three hypotheses that can serve as guideposts for research on plasticity in later age periods: First, likelihood, rate, and magnitude of plastic changes decrease after maturity. Second, when triggered, plastic changes often entail an overproduction of new synaptic connections, followed by pruning. Macroscopically, this sequence is associated with a pattern of gray matter volume expansion, followed by renormalization. Third, earlier plastic changes provide a structural scaffold for later learning. These hypotheses await empirical testing in humans, engender research design recommendations, and are related to fundamental open issues in research on human plasticity.

A Life-Span View of Structural Brain Plasticity

Life-Span Gradients in Plastic Potential

The term plasticity is often used interchangeably with learning, maturation, or adaptation. To avoid ambiguity that arises from such usage, I follow Lövdén et al. (2010) and define *plasticity* as the brain's capacity to respond

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

to environmental demands by triggering and implementing long-lasting structural changes that alter its functional and behavioral repertoire. I refer to the exploitation of that repertoire, or range of functioning, as *flexibility* (Lövdén et al. 2010). At the behavioral level of analysis, the distinction between plasticity and flexibility can be traced back to the Swiss psychologist and epistemologist Jean Piaget. Piaget argued that cognitive development alternates between phases of structural change, in which new structures and relations are created, and phases of elaboration, in which the implications of these structures and relations are explored and instantiated (Piaget 1980).

I posit that plasticity is triggered by a *mismatch between the current range of functioning and experienced demands*. To trigger and direct plastic changes, this mismatch between demand and supply needs to exceed the scope of the current repertoire while still being representable by the organism's nervous system (Figure 13.1). In addition, I postulate that plasticity is characterized by inertia. A central nervous system in a permanent state of plasticity-induced renovation would not be able to develop a coordinated set of habits and skills, and would constantly drain a large amount of precious metabolic resources (Kuzawa et al. 2014). Hence, demand–supply mismatches have to surpass some threshold of intensity and duration to trade the goal of stability for that of plasticity. This dynamic equilibrium shifts with age.

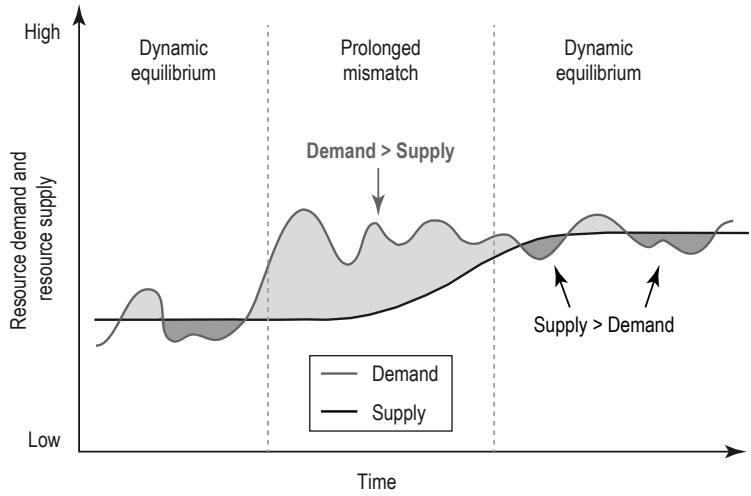

Figure 13.1 Supply–demand mismatch model of plasticity. The mismatch between functional supply and experienced environmental demands can be caused by primary changes in demand (shown here) or by primary changes in functional supply (not shown). Functional supply denotes structural constraints imposed by the brain on function and performance, and permits a given range of performance and functioning. Mismatches between supply and demand need to be present for some period of time to overcome the system's tendency toward stability (sluggishness) and to push the system away from its current dynamic equilibrium. Adapted after Lövdén et al. (2010).

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

Plasticity forms a necessary part of ontogeny in birds and mammals and establishes individuality (Freund et al. 2013). The evolving brain strikes a balance between plasticity and stability that supports the construction, modification, and maintenance of behavioral repertoires from early ontogeny into late adulthood. Over the course of their lives, humans acquire a rich model of the world that enables flexible deployment of established behavioral repertoires. For this reason alone, the number of situations requiring a plastic response is likely to decrease with advancing adult age. In addition, putting a premium on stability also favors continuity of social structures, which in turn may facilitate the deployment of plastic potential in the next generation (Lindenberger 2014). Finally, the metabolic costs of plasticity are likely to be amplified in neural systems that have accumulated damage, reflecting evolved limitations in somatic maintenance, as is the case for brains in later adulthood, when senescent changes become dominant. Primarily for these reasons, it can be assumed that the brains of older adults are both less capable and less in need of reacting to a supply–demand mismatch with a plastic response, as compared to the brains of typically developing children and adolescents. Hence the set point of the plasticity–stability equilibrium follows an overall life-span trend, moving from a greater relative emphasis on plasticity to a greater relative emphasis on stability (Lindenberger 2014).

There is evidence to support these claims. For a long time, plasticity was assumed to peak during critical periods early in life and to be absent thereafter. In contrast, early work in motor and auditory domains (Recanzone et al. 1993) as well as more recent studies have confirmed that plasticity is present throughout ontogeny, but to varying degrees and in different ways (Hensch 2005; Uhlhaas et al. 2010; Kempermann 2011; Hübener and Bonhoeffer 2014). In particular, there is accumulating evidence for experience-dependent plastic changes in the structure of the adult brain (Hübener and Bonhoeffer 2014), and these changes are large enough to be captured by magnetic resonance imaging (MRI) in adult humans (Draganski et al. 2004; for a review, see Lövdén et al. 2013). Using T_1-weighted MRI, gray matter alterations have been observed following extensive behavioral interventions, such as several months of juggling training, intensive studying for medical exams, foreign language acquisition studies, spatial navigation training (Lövdén et al. 2012; Wenger et al. 2012), playing video games (Kühn et al. 2014), and tracing with the nondominant hand (Wenger et al. 2017b). Other studies have reported gray matter changes after two weeks of mirror reading, seven days of juggling training, a few days of signature writing with the nondominant hand, and even after only two sessions of practice in a complex whole-body balancing task, or mere hours of training on color subcategories (for references, see Lövdén et al. 2013). Taken together, these results suggest that plastic changes in gray matter volume can emerge quite rapidly in adults. Note, however, that the method most commonly used to delineate these changes, voxel-based morphometry, does not permit firm conclusions about their physiological basis.

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

It is assumed that the dynamic interplay between mechanisms promoting plasticity and mechanisms promoting stability organizes behavioral development into alternating, sequentially structured periods that support the hierarchical organization of cerebral function and higher-order cognition (Figure 13.2). The canonical example is the sequence of critical periods that drive sensory and cognitive development from infancy to adolescence (Shrager and Johnson 1996; Hensch 2005; Hübener and Bonhoeffer 2010). Adopting knowledge about critical periods in early ontogeny may prove useful in understanding and, if deemed desirable, overcoming the greater inertia of the adult brain (Bavelier et al. 2010). Moreover, it is assumed that plasticity decreases further from early to late adulthood, reflecting senescent alterations of the brain involving reductions in energy metabolism, gray matter volume, white matter integrity, receptor densities, and neurotransmitter availability (Lindenberger 2014). Behavioral evidence is consistent with the prediction of life-span age gradients in plasticity (Brehmer et al. 2007, 2008; Schmiedek et al. 2010, 2014; see Figure 13.3). Eliciting plasticity in the adult brain may require shifting the excitatory–inhibitory circuit balance closer to levels present during critical periods in early ontogeny (Bavelier et al. 2010). In line with this notion, recent studies that modulated the excitability of motor cortex in adult humans with anodal transcranial direct-current stimulation have revealed improved learning (Hashemirad et al. 2016) along with reductions of the inhibitory neurotransmitter GABA (Stagg et al. 2009).

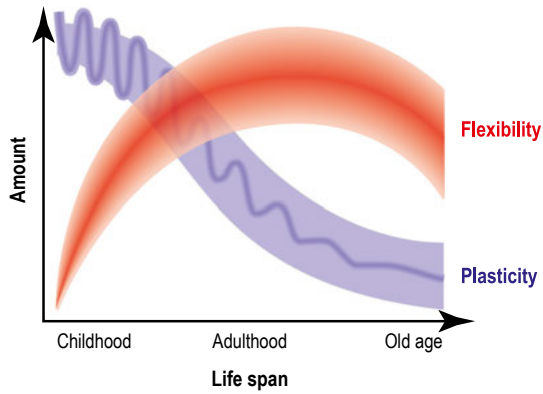

Figure 13.2 Plasticity and flexibility across the life span. *Plasticity* refers to long-lasting alterations in the brain's chemistry, gray matter, and structural connectivity in support of behavior. *Flexibility* denotes the capacity to optimize performance within the limits of the current functional supply. The dynamic interplay of mechanisms promoting plasticity versus stability, illustrated by the oscillating pattern of the plasticity trajectory, organizes behavioral development into alternating, sequentially structured periods that permit the hierarchical organization of cerebral function and higher-order cognition. The range of the functions at any give age denotes between-person differences and within-person modifiability. Reprinted with permission from Kühn and Lindenberger (2016).

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

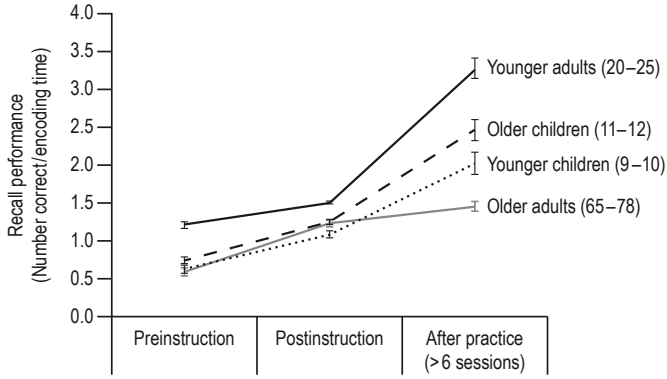

Figure 13.3 Life-span age differences in skilled memory performance. Individuals of different ages were instructed and trained in the Method of Loci, an imagery-based mnemonic technique. Recall performance is based on a ratio score of correctly recalled items over encoding time. Postinstruction scores for younger adults cannot be interpreted because of ceiling effects; all other data points can be interpreted. Error bars represent standard errors. Figure adapted after Brehmer et al. (2007).

In summary, converging evidence suggests that cortical plasticity is less easily activated through novel sensory and motor interactions with advancing age. Surprisingly, an experimental test of this hypothesis at the neural level in typically developing humans has thus far not been undertaken. Work by Brigitte Röder and others, however, provides supporting evidence from individuals with congenital sensory impairments (Nava and Röder 2011).

Dynamics of Plasticity: Overproduction–Pruning Model

Animal models have helped to uncover the dynamics of the molecular mechanisms that promote or suppress plasticity (Hensch 2005). In 1894, Santiago Ramón y Cajal proposed that mental activity might induce "novel intercellular connections through the new formation of collaterals and protoplasmic expansions." He then raised an intriguing question (Ramón y Cajal 1894:466; Azmitia 2007):

> One objection immediately presents itself: How can the volume of brain remain constant if there is a multiplication and even new formation of terminal branches of protoplasmic appendices and nerve collaterals?

On the ontogenetic timescale, the *pruning model of brain maturation* was proposed to offer an answer to Cajal's question (Changeux and Dehaene 1989). According to this model, an increase in the number of synapses is followed by experience-dependent selective stabilization of behaviorally relevant connections and the elimination of those connections that prove to be functionally irrelevant. Recent animal work provides a mechanistic basis for integrating microgenetic and ontogenetic timescales (Yang et al. 2009a), suggesting that

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

overproduction followed by pruning may point to a set of mechanisms that is common to all forms of plasticity.

Macroscopically, the pruning model leads to the expectation that plasticity is accompanied by an initial phase of volume expansion, followed by a phase of volume renormalization (Lindenberger et al. 2017; Wenger et al. 2017a). Animal work indicates that structural MRI methods should be capable of capturing such changes (Scholz et al. 2015). To observe the pattern of expansion and renormalization with greater precision in humans, voxel-based morphometry needs to be augmented by structural MRI methods that assess the thickness of the more heavily myelinated cortical laminae *in vivo*.

This expansion–renormalization pattern of plastic change is predicted by Darwinian accounts of cortical plasticity (Edelman 1987; Kilgard 2012) and neural development (Changeux and Dehaene 1989). The hypothesized pattern is also consistent with microscopic evidence which shows that plastic changes in sensory and motor cortex are marked by the rapid formation of new dendritic spines, followed by a slower process of spine elimination, almost returning the overall number of spines to pretraining levels (Hübener and Bonhoeffer 2014). For example, such rapid formation of new dendritic spines was observed in mice being trained to perform a reaching task (Xu et al. 2009). The rapid increase was followed by a slower process of elimination of spines that had existed before training, bringing the overall number of spines almost back to pretraining levels, while performance on the trained task remained high. Similarly, monkeys and rats learning to retrieve food showed training-related gray matter volume expansion that partially renormalized while behavioral performance remained stable (Molina-Luna et al. 2008; Quallo et al. 2009). Effects of exercise on progenitor cell proliferation have also been shown to follow an inverted U-shape (Kronenberg et al. 2006).

In relation to human data, we acquired up to 18 structural MRIs over a 7-week period while 15 right-handed participants practiced nondominant, left-hand writing and drawing (Wenger et al. 2017b). After four weeks of practice, increases in gray matter in both left and right primary motor cortices relative to a control group were observed; another three weeks later, these differences were no longer reliable. Time-series analyses revealed that gray matter in both primary motor cortices expanded during the first four weeks *and then partially renormalized, in particular in the right hemisphere, in the presence of continued practice and increasing task proficiency* (Figure 13.4).

It is worth noting that the present considerations call for a radical change in research designs to address plasticity in humans (Lindenberger et al. 2017). The pretest–posttest design, which implicitly equates structural plasticity with monotonic growth, has to be replaced by designs that capture nonmonotonic structural changes accompanying functional reorganization. Specifically, only research designs with multiple observations in the course of plastic change are able to detect and test the expansion–renormalization pattern, which posits a pattern of initial growth (e.g., overproduction of synaptic connections)

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

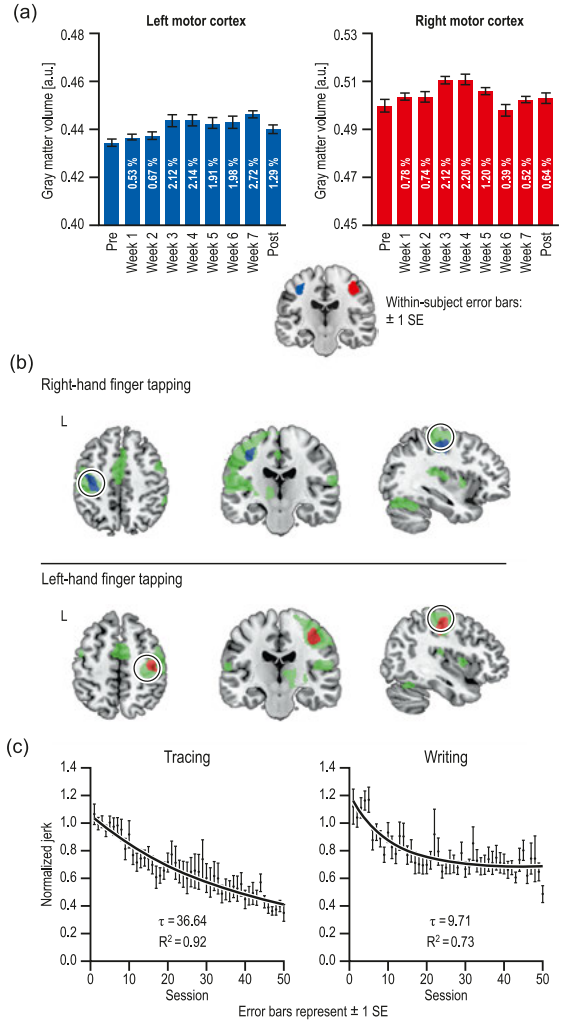

Figure 13.4 Evidence for the expansion–renormalization pattern during human skill acquisition. (a) In the course of left-hand training, gray matter volumes (measured in arbitrary units, a.u.) in the left and right primary motor cortices show initial expansion, followed by partial renormalization. (b) There is high spatial congruence between anatomical hand knobs, indicated by circles, and structural change as a function of left-hand training, displayed in blue and red for the left and right motor cortices, respectively. The functional activation maps during right-hand finger tapping and left-hand finger tapping are depicted in green. (c) Gains in left-hand tracing and writing during training. Normalized jerk is an index of movement smoothness. Individual training trajectories were fitted to exponential curves. Effects were quantified by the time constant τ of the exponential fit, indicating how fast participants approached the estimated asymptote, as well as relative improvement, expressed as R^2. Data shown here are averaged across all participants and displayed with error bars representing one standard error (SE) of the mean. Adapted after Wenger et al. (2017b).

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

followed by renormalization (e.g., pruning of these connections). As stated above, this model is based on physiological evidence, inspired by Darwinian concepts of cortical plasticity and neural development, and has never been tested in typically developing humans of different ages.

The overproduction–pruning model also speaks to concomitant changes in neural activation patterns and plasticity-induced network reorganization that are currently not well understood (see also section, Plasticity beyond Early Development: Open Issues). In line with Darwinian accounts of plasticity, task-related *functional* activations in cortical areas undergoing plastic reorganization should *increase* during the initial period of cortical expansion and *decrease* in the course of renormalization, when the pruning of new connections is likely to have led to sparser coding of task-relevant perception–action links, or schemata (Gdalyahu et al. 2012). Thus, the metabolic cost of plastic change is balanced by the benefit that a more efficient, metabolically less costly task representation is eventually achieved; more energy needs to be invested during the plastic episode to reach a metabolically more efficient state.

Primary Cortex Organization and Plasticity: Two Examples

Motor Cortex

Early research using low-intensity electrical stimulation led to the discovery of a somatotopically ordered representational map, or "homunculus," that resembled a distorted cartoon of the body. Later evidence confirmed the existence of functional subfields for legs, arms, and the head, but questioned the topographical representation of all body parts. As a prominent and undisputed part of the map, the cortical representation of motor hand functions is located in the superior part of the precentral gyrus, in a region labeled M1. Functional MRI work has delineated the human motor hand area as a knob-like field on the precentral gyrus. Typically, this field has an inverted omega shape and an extension of about 1.4 cm in the sagittal plane. Importantly, this topographical view of map organization has been complemented by the discovery of another organizing principle: a map of complex, meaningful movements or "ethological action maps" (Graziano 2016). The action map organization has been found in primates, prosimians, and rodents using a variety of stimulation, lesion, and neuronal recording methods.

Thus, the organization of M1 reflects the structures of both the body and its movement repertoire. Accordingly, motor skill acquisition consistently engages M1 (Dayan and Cohen 2011). It has been found that synaptogenesis induced by motor learning occurs in the same region in which learning-dependent alterations of the cortical map take place, indicating that motor skill acquisition is marked by the co-occurrence of functional reorganization and structural plasticity (Kleim et al. 2002). In support of this view, we observed

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

high spatial congruence between structural change, anatomical hand knobs, and functional activation patterns (Wenger et al. 2017b; see Figure 13.4b). Evidence from string players, correlated with the age at which they began to play their instruments, suggests that the plasticity of human motor cortex decreases from childhood to adolescence (Elbert et al. 1995). Further, experimental behavioral evidence indicates that motor skill acquisition decreases with advancing age (Ghisletta et al. 2010).

Primary Auditory Cortex

The tonotopic place–frequency code of auditory cortex originates in the inner ear's organ of Corti and is comparable to retinotopic and somatotopic representations. The core of the human auditory region comprises two fields that jointly fold across the transverse superior temporal gyrus, also known as Heschl's gyrus. The shape and size of these two fields varies between individuals (Gaser and Schlaug 2003). Both fields are organized by V-shaped tonotopic best-frequency gradients that can be mapped with fMRI using jittered tone sequences (Langers et al. 2014). Auditory plasticity decreases with age, but auditory maps retain some degree of plasticity throughout life. In adult animals, persistent exposure to random, band-limited, moderately loud sounds leads to changes in auditory cortex that are similar to those observed after restricted hearing loss (Pienkowski and Eggermont 2011). I hypothesize that learning to discriminate increasingly small pitch intervals may lead to a more fine-grained representation of frequencies in primary auditory cortex, and hence to changes in best-frequency gradients that are discernible with fMRI-based tonotopic mapping.

A Note on Plastic Changes in Primary Cortical Areas

Learning-induced improvements in perceptual thresholds and motor skills have often been attributed to an increase in the extension of sensory or motor cortical maps. However, it is worth noting that plastic changes *within* cortical maps are not necessarily associated with changes in the *extension* of this map. From the perspective of the expansion–renormalization model (Lövdén et al. 2013; Wenger et al. 2017a), an overproduction of neural connections can lead to a *transient local thickening of deeper cortical layers which may or may not trigger changes in the size of the map*. Recently proposed MRI protocols gauging the thickness of myelinated layers of the cortex are likely to capture such localized plastic changes in humans.

Plasticity Effects on Later Learning

An intriguing finding in plasticity research concerns the physiological basis of the effects of earlier episodes of plasticity on later learning. It has been

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

observed that the malleability and later preservation of postsynaptic spines on apical dendrites of pyramidal neurons in layer V serve as mechanisms to encode and store new experiences in cortical circuits (Yang et al. 2009a; Hofer and Bonhoeffer 2010; Hübener and Bonhoeffer 2010; Meyer et al. 2014). A remarkable example is the formation and elimination of dendritic spines during motor skill acquisition in rodents (Yang et al. 2009a). Importantly, Yang et al. (2009a) found that a small fraction of new spines were preserved and appeared to provide the structural substrate for memory retention throughout the animal's lifetime. Thus, plastic changes during skill acquisition form lifelong memories that are stored in stably connected neural networks, or plasticity-induced engrams (Hofer and Bonhoeffer 2010; Tonegawa et al. 2015).

This microscopic evidence on engram formation is of great importance and warrants the hypothesis that the *expansion–renormalization pattern indicative of plasticity will be reduced or absent when a previously acquired skill is reactivated and learning is resumed, after a break, on a task that has previously elicited plastic change*. In terms of our theoretical framework (Lövdén et al. 2010), this would mean that skill acquisition elicits plasticity, whereas skill reactivation, in its extreme form, draws on existing structures, and requires flexibility. I hypothesize that the lack of a need for plasticity during skill reactivation, and hence the minimization or absence of the expansion–renormalization pattern, depends on three factors:

1. The age at which the skill has been originally acquired, in the sense that plasticity at younger ages, or during age periods falling into a critical period, leads to more durable engrams, hence reducing the need for plasticity when the skill is reactivated at an older age (see Figure 13.5).
2. The age at which the skill is reactivated, in the sense that plasticity is reduced at older ages (e.g., in late adulthood).
3. The time period elapsing between initial acquisition and reactivation, in the sense that plasticity-induced engrams may deteriorate with age, in particular when they were acquired during later periods of ontogeny.

In line with these considerations, human behavioral evidence suggests that the positive effects of plasticity on later learning decline with age (Brehmer et al. 2008; Schmiedek et al. 2014).

Individual Differences in Plasticity

Individual Differences in Skill Acquisition

The primary cortices form part of a structured learning architecture (Chein and Schneider 2012). Networks that generate and monitor new behavioral routines and action sequences also belong to this architecture and contribute to individual differences in skill acquisition. It is assumed that a network, sometimes

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

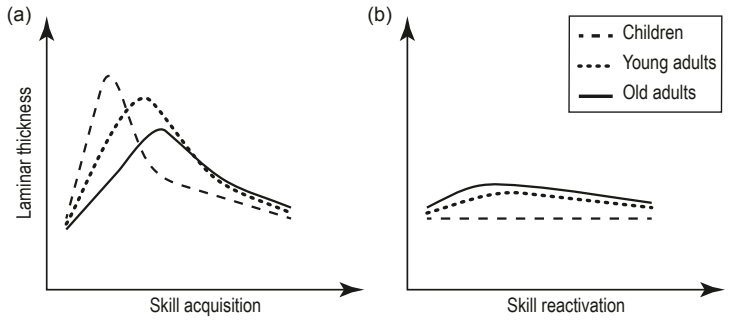

Figure 13.5 Hypothesized age differences in expansion and renormalization during (a) skill acquisition and (b) skill reactivation. Both the degree of plasticity and the durability of plasticity-induced engrams are assumed to decline with age. Hence skill reactivation after a constant time period is in greater need of plasticity if the skill was originally acquired at a later age. Predictions are based on the expansion–renormalization model, and on animal models indicating that stably maintained dendritic spines in layer V of primary cortex serve as a substrate for memory.

designated as the metacognitive system (Chein and Schneider 2012), notes and keeps track of the mismatch in supply and demand that triggers plasticity. It follows that reductions in that mismatch due to improvements in task performance should be accompanied by decreasing activations of prefrontal and temporal brain areas, which are critically involved in the metacognitive system. Repeated MRI scans during skill acquisition, as carried out by Wenger et al. (2017b), would permit researchers to quantify age group differences, as well as individual differences within age groups, in the expression of the expansion–renormalization pattern, as a quantitative index of plasticity in primary cortical areas, along with associated changes in functional activation patterns during task performance.

Individual Differences in Plasticity

Plasticity differs greatly among people of the same age (Brehmer et al. 2007; Mårtensson et al. 2012; see also Figure 13.6). However, the physiological predictors of between-person differences in plasticity remain poorly understood. Below, I outline some antecedents and correlates of individual differences in plasticity that await further study.

First, given that the formation of new neural connections is metabolically costly (Kuzawa et al. 2014), one may expect that general individual differences in brain metabolism predict differences in plasticity; a metabolically more resourceful brain should be more likely to shift from a stability to a plasticity regime than a metabolically less resourceful brain. Second, individual differences in plasticity within specific domains, such as auditory pitch discrimination, are likely linked to preexisting differences in brain anatomy,

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

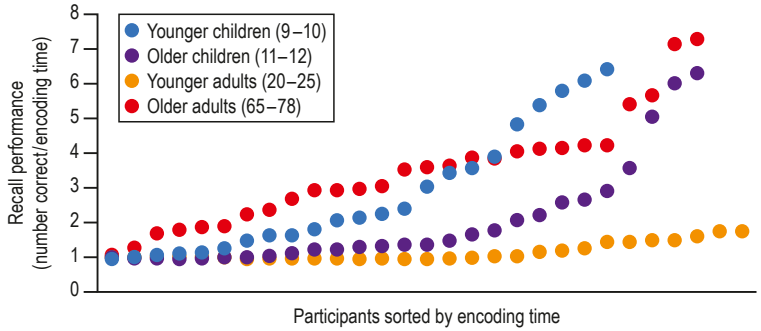

Figure 13.6 Individual differences in plasticity within age groups. The figure refers to performance after practice, illustrated in Figure 13.3, and shows the adaptively determined encoding times needed by individual participants to recall an average of 57 out of 96 words distributed across 6 lists of 16 words. Individuals are sorted by encoding time. In children, encoding times ranged from 1–7.2 seconds per word. Figure adapted after Brehmer et al. (2007).

such as the morphology of primary auditory cortex (Gaser and Schlaug 2003). Furthermore, a reliable portion of individual differences in plasticity is associated with genetic differences; for instance, behavioral and genetic evidence indicates that genetic variation in individuals' musical abilities affects both the ability and the inclination to practice, such that music practice in itself does not add unique variance to individual differences in musical ability (Mosing et al. 2014). At the molecular levels, a range of single nucleotide polymorphisms (SNPs) has been tentatively related to individual differences in plasticity (Lövdén et al. 2011; Bellander et al. 2015). Candidate gene or genome-wide association approaches could be used to examine the unique and interactive effects of SNPs that result in individual differences in transmitter systems known to affect excitatory–inhibitory balance in primary cortical areas, such as glutamate, GABA, and dopamine. Finally, in terms of epigenetics, it seems worthwhile to examine differences in DNA methylation affecting the expression of plasticity-related genes during skill acquisition versus skill reactivation, with the caveat that DNA methylation markers obtained outside the brain (e.g., via buccal swabs) may not be indicative of DNA methylation in the brain.

Below I will outline a set of research hypotheses that derive directly from the framework just outlined. This will be followed by a discussion of open issues, speculative in nature and only loosely connected to the framework.

Plasticity beyond Early Development: A Set of Research Hypotheses

Life-Span Differences in the Plasticity of Primary Cortices

Hypothesis 1: Life-span gradients in plasticity. The plasticity of motor and auditory cortices in response to experience is greatest in children and smallest

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

in older adults, with younger adults falling in between (Figure 13.5a). This hypothesis corresponds to a long-standing claim of life-span psychology (Baltes et al. 2006; Lindenberger 2014) that has thus far not been tested experimentally in typically developing humans.

Delineating the Expansion–Renormalization Pattern of Plastic Change

Hypothesis 2a: Plasticity is expressed by nonmonotonic volume changes in primary cortices. The task-relevant deeper laminae of primary cortices will show a pattern of initial expansion, reflecting the formation of new neural connections, followed by renormalization, reflecting subsequent pruning. This hypothesis is consistent with microscopic findings in animals and informed by Darwinian models of plasticity and development (Changeux and Dehaene 1989; Kilgard 2012).

Hypothesis 2b: Plasticity leads to sparsification of the neural code. During later periods of a plastic episode, brain activation will decrease while performance will continue to improve, reflecting sparsification of the neural code. This hypothesis is based on the assumption that plastic change, if successful, results in a metabolically efficient neural representation of the trained task.

Testing the "Memory of Plasticity" or the Effects of Plasticity on Later Learning

Hypothesis 3a: Plasticity-induced structural alterations are partially preserved and serve as a scaffold for later learning. The expansion–renormalization pattern will be attenuated or absent when a previously acquired skill is reactivated at a later point in time, reflecting the stability of previously formed neural connections.

Hypothesis 3b: The preservation of plasticity-induced structural alterations decreases with age. We assume that the mechanisms that stabilize newly formed synaptic connections in cortical circuits (Meyer et al. 2014; Tonegawa et al. 2015) decrease in efficiency with advancing age. Hence the reduction of the expansion–renormalization pattern when a sensory or motor skill is reactivated after a constant period of time will be greatest in children and smallest in older adults, with younger adults falling in between (Figure 13.5b). This finding would corroborate the widely held but untested claim that the positive effects of plasticity on later learning decline in the course of ontogeny.

Individual Differences in Plasticity and Skill Acquisition

Hypothesis 4a: Individual differences in primary cortex plasticity, learning rates, and final task proficiency form a positive manifold and contribute to gene–environment correlations (Beam and Turkheimer 2013); see also Hypothesis 4d.

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

Hypothesis 4b: The contribution of the metacognitive network to task performance will decrease with practice. Individual differences in this decrease will be positively related to skill acquisition, reflecting less effortful and more efficient performance.

Hypothesis 4c: Individual differences in the expression of the expansion–renormalization pattern will show positive associations with skill acquisition. It is assumed that initial overproduction and pruning both contribute to plastic change, akin to mutation and selection on an evolutionary timescale.

Hypothesis 4d: Individual differences in metabolic, anatomic, and genetic markers predict differences in plastic responses to experience. The following exemplary predictions emanate from this generic hypothesis:

1. Individual differences in brain metabolism can serve as trait markers of plastic potential.
2. Preexisting differences in the anatomy of primary auditory cortex selectively predict plasticity in the auditory domain.
3. SNPs related to individual differences in GABA and glutamate expression are associated with experience-induced shifts in excitatory–inhibitory balance, which in turn predict laminar expansion and renormalization.
4. Genes identified previously as being relevant for plasticity, such as the BDNF gene and dopamine-related genes, predict individual differences in plasticity within age groups, especially in old age, when brain resources are scarce (Papenberg et al. 2015).
5. Periods of skill acquisition marked by expansion–renormalization of primary cortical areas will be associated with changes in DNA methylation status (Guo et al. 2011).

Plasticity beyond Early Development: Open Issues

The purpose of this final section is to raise issues of general importance for the age-comparative study of human plasticity. Many of these are not yet sufficiently well understood to permit the operational definition of testable hypotheses. Rather, they are meant to serve as guideposts for future conceptual and empirical efforts in the study of human plasticity.

Issue 1: We need to be aware of the almost ubiquitous and often unavoidable confound between age and experience whenever we wish to make claims about age differences in plastic potential. Individual development reflects age-graded changes in the interactions among maturation, residues of earlier learning (e.g., memories of all kinds), senescence, and new learning. Hence, manifest age differences in plasticity may not solely reflect age-graded differences in plastic potential but rather a variety of additional influences that interact in unknown

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

ways with plastic potential. In particular, memories, or the sediments of past learning, accumulate with age. Even a system whose plastic potential does not decline with age would experience fewer and fewer episodes of plastic change with increasing age for the simple reason that the accumulation of experience makes it increasingly difficult to experience an environmental demand characteristic for the first time.

Issue 2: We need a better understanding of how age-based changes and between-person differences in large-scale network topography affect the context for local plastic change. Cognitive development from childhood to adulthood is accompanied by profound changes in structural and functional connectivity (Uhlhaas et al. 2010), presumably associated with declines in general synchronizability and increases in controllability (Tang et al. 2017). Hence the cerebral context for acquiring any given skill changes with age, and these changes may affect the plasticity of cortical areas in unknown ways. In particular, the maturation of the parietal and prefrontal cortices during childhood and adolescence and the growing number of available skills and bodies of declarative knowledge (see Issue 1) lead to an increase in top-down strategic control over perceptual processes with advancing age. This increase in control may help specify the supply–demand mismatch and hence direct attention to specific aspects of behavior that are in need of plastic change. This increase, however, may also hinder local plastic change through an excessive strategic guidance of local overproduction–pruning dynamics. For instance, although directing attention toward a to-be-acquired skill may generally be helpful, overly precise knowledge about what should be done to acquire it may lead to an "over-instruction" of local circuits that hinders local plastic change.

Issue 3: We need a mechanistic account of the plasticity of higher-order cognition. In this chapter, research on critical periods of perceptual and motor skills during early development was used as a template to delineate a research program on human plasticity across the life span. This strategy reflects the premise that human research on plasticity needs a strong connection and a firm grounding in animal models. In particular, optogenetic tools and two-photon microscopy have provided insights into the molecular dynamics of plastic changes that need to be brought to bear upon research in humans. At the same time, we need to be cautious. We do not know the extent to which plasticity observed in primary sensory and motor cortices in the context of perceptual and motor skill acquisition offers a viable analogy to the role of the association cortices in the context of higher-order cognitive abilities such as episodic memory, working memory, task-set switching, and fluid intelligence. Similar to the plasticity of perceptual and motor skills, the plasticity of these abilities, if present, is likely to require a mixture of local plastic change (e.g., akin to cortical map extension in the primary cortices) and more global changes such as myelination of relevant white-matter tracts in the service of network reorganization (e.g., to improve synchronization of posterior and anterior regions). However, with the exception of the role of the hippocampus in

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

memory and related functions, the relative importance of local plastic change for higher-order cognitive abilities is not well understood. Can we target a higher-order cognitive function, such as efficient switching between task sets, and identify a cortical area, or set areas, that shows the expansion–renormalization pattern when this function is trained? Or is improvement of higher-order cognitive abilities, especially in adulthood, generally more a matter of flexibility than of plasticity, in the sense that the behavioral repertoire available to the system is exploited more fully and reconfigured more efficiently without any structural change?

Issue 4: We lack neural theories of generalization and transfer to predict consequences of plastic change. In recent years, the issue of transfer of training attracted great scientific and public interest (Simons et al. 2016), with much of the debate focused on whether the effect sizes of transfer of training do, in some cases, differ from zero. Unfounded claims about real-life benefits of "brain jogging" abound[1] while attempts to use mechanistic accounts of plastic change for deriving hypotheses about generalization and transfer (Dahlin et al. 2008) are scarce. Clearly, a better understanding of plasticity in humans is a prerequisite for arriving at hypotheses about transfer gradients and generalization (Lindenberger et al. 2017). This is especially true for higher-order cognitive functions (see Issue 3), where we lack evidence on the processes associated with plastic change.

Issue 5: We need a better understanding of the relationship between brain size and neural efficiency. General cognitive ability shows a weak to moderate positive association with brain size (Luders et al. 2009). For instance, a recent meta-analysis found that larger prefrontal cortex volume and greater prefrontal cortex thickness are associated with better executive performance (Yuan and Raz 2014). Apparently, then, both neural code efficiency and brain size determine an individual's effective "functional cerebral space" (Kinsbourne and Hicks 1978). However, the recursive relations between size and efficiency are not well understood. For instance, size may enable efficiency, or efficiency may alleviate the effects of smaller size.

Recommendations for Future Research

What all these open issues have in common is that they can only be tackled successfully if research on plasticity in humans goes beyond the pretest–posttest design (Lindenberger et al. 2017). To understand plastic change in humans, we first need to observe it using imaging protocols that facilitate mechanistic interpretation. As a critically important step toward this goal, we need research

[1] For a critique, see "A Consensus on the Brain Training Industry from the Scientific Community," Max Planck Institute for Human Development and Stanford Center on Longevity, http://longevity.stanford.edu/a-consensus-on-the-brain-training-industry-from-the-scientific-community-2/ (accessed Oct. 11, 2017).

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

with rodents and nonhuman primates using optogenetic and MRI methods in combination to inform the interpretation of MRI results obtained in research with humans (Lerch et al. 2017). Investigating the dynamics and temporal progression of plastic change in humans requires experiments with multiple imaging sessions during # that include a selection from a wide range of imaging modalities (e.g., structural and functional MR as well as MR spectroscopy) to assess metabolites such as GABA, glutamate, and creatine, as well as electrophysiological recordings (e.g., electroencephalography, magnetoencephalography, and intracranial recordings) to assess related changes in oscillatory patterns. If motivated by a search for mechanisms of plastic change, the repeated application of these methods *in the context of age-comparative high-intensity training studies* bears great promise for the future of plasticity research.

These empirical efforts will benefit from close interactions with work on neuromimetic computational architectures and machine-learning algorithms (LeCun et al. 2015; Mnih et al. 2015). Building on pioneering work by Terry Sejnowski, Jay McClelland, Mark Johnson, and others (Sejnowski et al. 1990; Elman et al. 1996; McClelland 1996; Shrager and Johnson 1996), such artificial systems enable researchers to observe the dynamics of plastic change within and between the layers of artificial neural networks, and hence can guide them in formulating and testing hypotheses about developing biological systems.

Acknowledgments

The author thanks Julia Delius for her editorial contributions as well as Simone Kühn, Martin Lövdén, Naftali Raz, and Elisabeth Wenger for valuable discussions that contributed to the conceptual framework and helped to improve this chapter. Preparation of this chapter was facilitated by a Fernand Braudel Senior Fellowship of the European University Institute to Ulman Lindenberger.

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.