ANNUAL REVIEWS

Annual Review of Developmental Psychology

Brain Plasticity in Human Lifespan Development: The Exploration–Selection–Refinement Model

Ulman Lindenberger[1,2] and Martin Lövdén[3]

[1]Center for Lifespan Psychology, Max Planck Institute for Human Development, 14195 Berlin, Germany; email: seklindenberger@mpib-berlin.mpg.de

[2]Max Planck UCL Centre for Computational Psychiatry and Ageing Research, 14195 Berlin, Germany, and London WC1B 5EH, United Kingdom

[3]Aging Research Center, Karolinska Institutet and Stockholm University, SE-171 77 Stockholm, Sweden; email: martin.lovden@ki.se

Annu. Rev. Dev. Psychol. 2019. 1:197–222

First published as a Review in Advance on December 12, 2019

The *Annual Review of Developmental Psychology* is online at devpsych.annualreviews.org

https://doi.org/10.1146/annurev-devpsych-121318-085229

Keywords

development, plasticity, exploration, lifespan, transfer, reinforcement learning

Abstract

Plasticity can be defined as the brain's capacity to achieve lasting structural changes in response to environmental demands that are not fully met by the organism's current functional capacity. Plasticity is triggered when experiential forces interact with genetic programs in the maturation of species-common functions (e.g., vision), but it is also required for less universal forms of learning that sculpt individuals into unique members of their species. Hence, delineating the mechanisms that regulate plasticity is critical for understanding human ontogeny. Nevertheless, mechanisms of plasticity in the human brain and their relations to individual differences in learning and lifespan development are not well understood. Drawing on animal models, developmental theory, and concepts from reinforcement learning, we introduce the exploration–selection–refinement (ESR) model of human brain plasticity. According to this model, neuronal microcircuits potentially capable of implementing the computations needed for executing a task are, early in learning, widely probed and therefore structurally altered. This phase of

exploration is followed by phases of experience-dependent selection and refinement of reinforced microcircuits and the concomitant gradual elimination of novel structures associated with unselected circuits. The ESR model makes a number of predictions that are testable in humans and has implications for the study of individual differences in lifespan development.

Contents

INTRODUCTION

In this article, we outline the central role of plasticity in human development. We then discuss recent work on human plasticity, arguing that lack of theory and a premature focus on application might have hindered progress in understanding the underlying neural processes. Next, we turn to animal models of plasticity and propose that this body of work, together with initial evidence in humans, is consistent with the exploration–selection–refinement (ESR) model of brain plasticity. We formulate hypotheses on the basis of the ESR model that are testable in humans and explore its utility for understanding individual differences in cognitive development.

THE ROLE OF PLASTICITY IN HUMAN DEVELOPMENT

Development Across the Lifespan

Developmental psychology seeks to identify mechanisms that generate invariance and variability as well as constancy and change in behavioral repertoires from fetal development to old age

(Lindenberger et al. 2006, Newcombe 2011). By identifying the commonalities, differences, and interrelations in the ontogeny of functional domains, such as perception, motor skills, and cognition, within and across individuals, developmental psychologists strive to formulate general theories of behavioral development (Baltes et al. 2006). In order to provide explanations that qualify as psychological, neuronal, and developmental, the effects of external forces, such as participation in the educational system (Lövdén et al. 2020) or in a motor skill training program (Wenger et al. 2017b), need to be mapped onto mechanisms and laws that operate and evolve within developing individuals (Newcombe 2011).

Individuals' exchange with the physical and social environment is dynamic and recursive (**Figure 1**) (Li 2003, Lindenberger et al. 2006). On the one hand, the changing brain and the changing physical and cultural environment shape behavioral development. On the other hand, behavior alters the brain and the social and physical aspects of the environment. Thus, environment and brain act both as antecedents and as consequents of moment-to-moment variability and long-term changes in patterns of behavior. The components of this system—brain, behavior, and environment—are intertwined; none of the three components can be reduced to either of the other two (Krakauer et al. 2017, Schaie 1962).

In attempts to explain the development of this system, maturation and senescence denote the operation of mechanisms and their effects on changes in behavior that are especially pronounced early and late in life, respectively (Lindenberger 2014, Lindenberger et al. 2006). Maturation is under strong evolutionary control (Kirkwood 2005) and refers to the orderly and genetically orchestrated construction of neural structures from conception to adulthood that enable reproductive success (Elman et al. 1996). In contrast, human senescence is likely to reflect evolved limitations in somatic maintenance, resulting in an accumulation of damage and the unwarranted continuation of biological programs that were vital in early development but become useless or harmful in the postreproductive period (Baltes 1997, Blagosklonny & Hall 2009, Kirkwood 2005). In the absence of programmed aging, modifiers and modulators come to the fore, and individual differences abound (Raz & Daugherty 2018).

Notably, processes commonly associated with maturation are not confined to early ontogeny, and processes related to senescence are not restricted to old and very old age. For instance, neurogenesis and synaptogenesis continue in the aging human brain (Snyder 2019). Conversely, declines in dopaminergic neuromodulation, which indicate senescence-related changes in brain chemistry, commence in early adulthood (Bäckman et al. 2010). Also, the ways in which senescence takes its toll on the brains of aging individuals may depend on individuals' experiential and maturational histories (Cabeza et al. 2018, Koen & Rugg 2019).

Plasticity: A Fundamental Capacity for Individual Development

Maturation is intertwined with plasticity (Elman et al. 1996, Newcombe 2011). We define plasticity as the brain's capacity to implement lasting structural changes that alter its functional and behavioral repertoire and are triggered in response to environmental demands that are not fully met by the organism (Kühn & Lindenberger 2016; Lindenberger 2018; Lindenberger et al. 2017; Lövdén et al. 2010a, 2013). Plasticity is not a unitary phenomenon and, according to Greenough et al. (1987), comes in two distinct types. One is experience-expectant plasticity, which enables organisms to meet species-specific experiences that allow for functional development, be it imprinting (Lorenz 1937) or the development of basic sensory functions such as vision (Wiesel & Hubel 1963). The close link between maturation and plasticity is evident in this form of plasticity. The other type is experience-dependent plasticity, which enables an individual to respond and adapt to idiosyncratic changes in the environment. It is considered to be driven by learning,

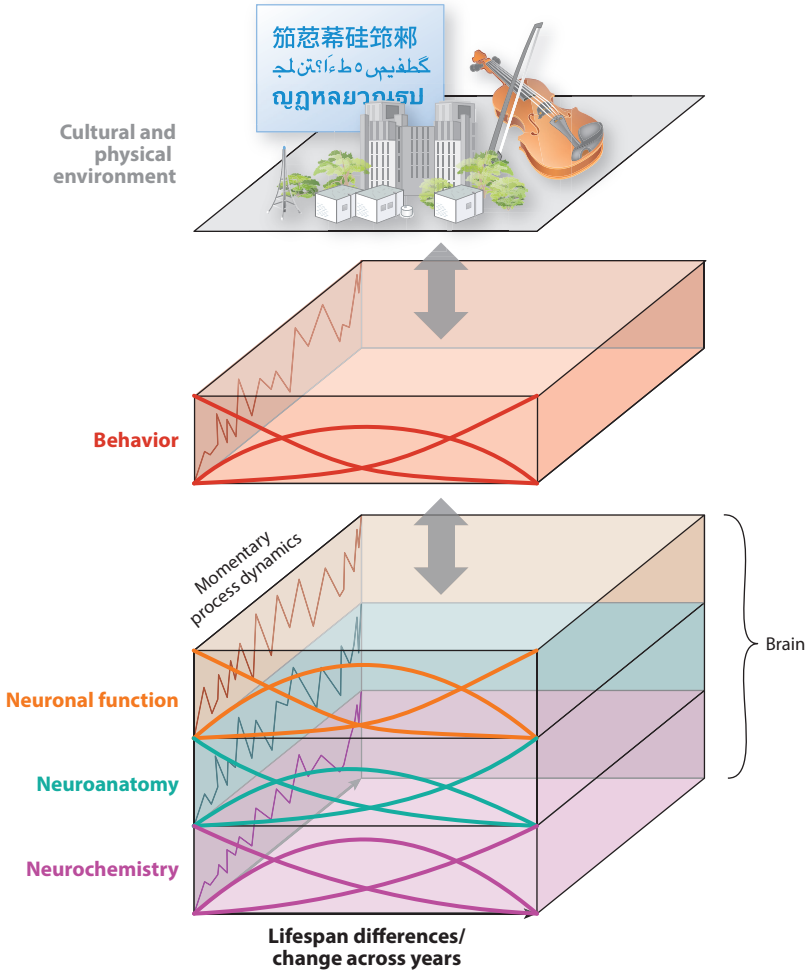

Figure 1

Environment and brain as antecedents and consequents of moment-to-moment variability and long-term changes in patterns of behavior. Lifespan changes in brain–behavior mappings are shaped by interactions among processes related to maturation, learning, and senescence. The identification of key players in the ontogeny of brain–behavior dynamics requires a coalition between formal tools for synthesis across levels of analysis and timescales as well as empirical methods to study variability and change in brain and behavior. Figure adapted with permission from Lindenberger et al. (2006).

denoting the process of constructing, through experience, new brain states that represent novel or modified knowledge, skills, and values. However, learning also provides a viable account of processes involved in experience-expectant plasticity. Given that the ability to acquire specific skills that are idiosyncratic to the environmental niche of a given individual also represents an adaptation that has resulted from natural selection, the mechanisms implementing either type of plasticity may resemble one another. Thus, the distinction between experience expectancy and experience dependency may reflect gradual differences in the scope and developmental timing of plastic episodes, rather than two distinct categories.

Plasticity Versus Stability

Plasticity is not all good or all bad, and there must be some homeostatic sweet spot between plasticity and stability, such that the brain is not under costly and permanent renovation that would compromise a competing need for constancy. Hence, the brain's potential for plasticity is actively held in check by mechanisms that sustain stability (Clopath et al. 2017, Hensch 2004, Hübener & Bonhoeffer 2014). This dynamic interplay of plasticity and stability mechanisms organizes behavioral development into multiple alternating periods of plasticity and relative stability that enable the hierarchical and specialized organization of cerebral function and behavior (Kühn & Lindenberger 2016, Lindenberger 2018, Takesian & Hensch 2013). Of course, such alternations do not affect the entire brain at the same time; instead, they vary in timing, brain areas, and behavioral function (Bourgeois 1997, Panchanathan & Frankenhuis 2016, Tau & Peterson 2010).

During periods of stability, defined as absence of plastic changes, behavior is far from immutable: In addition to plasticity, there is flexibility, which we define as the adaptive reconfiguration of the existing behavioral repertoire in the absence of long-lasting structural change (Lövdén et al. 2010a, Medaglia et al. 2018). At the behavioral level of analysis, the distinction between plasticity and flexibility can be traced back to Jean Piaget (1980), who 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.

Lövdén et al. (2010a) proposed the economic metaphor of neural supplies and experiential demands to further clarify the difference between plasticity and flexibility. Whereas flexibility exploits existing neural supplies (i.e., an organism's current functional capacity), plasticity changes them. It would be functionally maladaptive and metabolically costly if a system were always to be responding instantaneously to supply–demand mismatches with plastic changes rather than utilizing the range of function supported by flexibility. A central nervous system under permanent renovation would not develop a coordinated scheme of habits and skills, and would constantly consume large amounts of energy, eventually reducing evolutionary fitness (Mery & Kawecki 2003). Thus, the supply–demand mismatch has to surpass some degree of intensity to trade the goal of stability for that of plasticity. The degree of sluggishness of plastic responses to mismatch differs among various manifestations of plasticity, probably partly as a function of their metabolic implementation costs (Blair et al. 2020, Kuzawa et al. 2014). For example, whereas gliogenesis and growth of capillaries may develop over months, synaptogenesis, spine formation and modification, and structural changes associated with long-term potentiation may develop over hours, minutes, or seconds.

In the course of their lives, adults acquire a rich model of the world that enables the 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 favors continuity of social structures, which in turn may facilitate the deployment of plastic potential in the next generation (Lindenberger 2014). Finally, the metabolic cost of plasticity is likely to be exacerbated in older individuals who have accumulated damage, reflecting evolved limitations in somatic maintenance (Raz & Daugherty 2018). Primarily for these reasons, we assume that the brains of older adults are less able to react to a supply–demand mismatch with a plastic response, relative to the brains of normally developing children and adolescents, and are also less in need of doing so (Baltes & Kliegl 1992; Brehmer et al. 2007, 2008; Lövdén et al. 2012a; Zinke et al. 2014).

In summary, developing brains strike a balance between plasticity and stability that supports the construction, modification, and articulation of behavioral repertoires across the lifespan

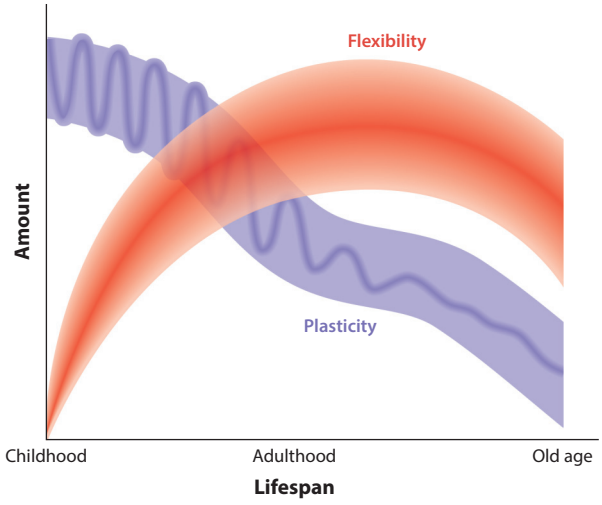

Figure 2

Plasticity and flexibility across the lifespan. 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 development into multiple alternating and sequentially structured periods that support the hierarchical organization of cerebral functions and behavior. Figure adapted with permission from Kühn & Lindenberger (2016).

(**Figure 2**). In particular, the transition from childhood to adulthood strengthens the mechanisms that actively suppress plasticity and promote stability. We assume that the set point of the plasticity–stability equilibrium follows an overall lifespan trend from a greater relative emphasis on plasticity to a greater relative emphasis on stability. The peak age of flexibility varies from domain to domain, and is likely to reflect the net result of two opposing and interacting forces: the cumulative effects of plastic episodes, on the one hand, and the increasingly strong effects of senescence, on the other. While these considerations match current knowledge, it is worth noting that systematic empirical work on lifespan differences in behavioral and neural manifestations of plasticity is scarce and difficult to conduct (Walhovd & Lövdén 2020).

Human Brain Plasticity: Moving Toward a Theory of Change

Cognitive intervention studies, such as those requiring practice on cognitive tasks, are probes of plasticity that invariably lead to performance gains on the trained tasks (Donner & Hardy 2015, Newell & Rosenbloom 1981). Acknowledging the profound influence of plasticity on individual differences in behavioral development across the lifespan, an increasing number of researchers have explored the potential of such interventions for applied purposes. In much of this work, the generality or range of practice-related performance gains has been at the center of attention. One way to examine generality is to administer tasks that share critical features with the trained task before and after the intervention, and to assess whether improvements on the trained task transfer to these other tasks, both relative to an untrained control group and in terms of dose–response relations within the trained group, such that individuals with greater gains on the trained task also show greater gains on the transfer task. To be meaningful, this research strategy requires models of change that specify which parts of the cognitive system have been altered through experience, and

which of the parts that have been altered in this way are shared between trained and transfer tasks (Baltes et al. 1988, Lövdén et al. 2010a, Noack et al. 2014, Thorndike 1898). Furthermore, standard psychometric criteria of validity and reliability, which are difficult to attain in the measurement of change, need to be met when assessing transfer (Brandmaier et al. 2018a, Kievit et al. 2018, Noack et al. 2014). This observation also applies at the neural level, where basic information about reliability is often lacking (but see Brandmaier et al. 2018b, Gordon et al. 2017, Karch et al. 2019, Oschwald et al. 2019).

Unfortunately, models of change are notoriously difficult to formulate and operationalize, as they need to combine detailed knowledge about the mechanisms and components of change with detailed knowledge about the demand characteristics of the tasks involved. For instance, practicing tasks that critically depend on working memory may show, or fail to show, transfer to untrained tasks involving working memory and related abilities such as fluid intelligence for a variety of reasons, including the presence or absence of changes in processing efficiency, capacity, and speed–accuracy trade-offs, as well as surface similarities between the trained task and the transfer task. Discriminating among these reasons without a theoretically motivated and empirically testable model of change and related task analyses is dubious (von Bastian & Oberauer 2014).

At the neural level, plasticity is present throughout the lifespan, to different degrees and in different ways (Knudsen 1998, Kühn & Lindenberger 2016, Takesian & Hensch 2013). In humans, gray matter increases have been observed after several months of juggling training, intensive studying for medical exams, foreign language acquisition, spatial navigation training, playing video games, and tracing with the nondominant hand (Draganski et al. 2004; Draganski & May 2008; Kühn et al. 2013, 2014; Lövdén et al. 2010b, 2012b; McNab et al. 2009; for a summary, see Wenger et al. 2017a). These observations at the neural level have fostered initial optimism that the effects of cognitive training on behavior may generalize beyond the trained task and improve cognitive abilities. This optimism has been considerably dampened by recent meta-analyses and reviews, which indicate that behavioral transfer effects are generally either absent or small and relatively narrow in scope (Bediou et al. 2018, Hilgard et al. 2019, Lövdén et al. 2013, Melby-Lervåg & Hulme 2016, Melby-Lervåg et al. 2016, Noack et al. 2014, Simons et al. 2016, von Bastian & Oberauer 2014). The commonly reported specificity of performance gains induced by cognitive training stands in contrast to physical exercise interventions, which can enhance processing capacity through mechanisms that broadly affect cognition, such as improved vascularization and the release of growth factors (Voss et al. 2013).

In a uniquely extensive training study (Schmiedek et al. 2010), older and younger adults practiced three working memory, three episodic memory, and six perceptual speed tasks for 100 1-h sessions. Immediately after training, both older and younger adults showed modest near transfer of training to latent ability factors of working memory (net effect sizes, $d = 0.36$ and $d = 0.31$, respectively). In addition, younger adults showed moderate transfer to latent ability factors of episodic memory ($d = 0.51$) and weak transfer to reasoning ($d = 0.19$). Neural data obtained for subsamples of both younger and older adults revealed an increase in a potential indicator of white matter integrity in the genu of the corpus callosum (Lövdén et al. 2010b) and attenuated cerebellar shrinkage (Raz et al. 2013). However, there were no indications of correlational links between changes in physiology and performance changes on the trained tasks or the transfer tasks within the training groups. Also, in older adults, transfer effects were no longer measurable when individuals were tested again two years later; in younger adults, transfer effects for latent factors of reasoning ($d = 0.23$) and episodic memory ($d = 0.18$) were maintained (Schmiedek et al. 2014). The results of this massive intervention study show that large amounts of training can yield transfer effects. The observed transfer effects were limited in size and duration, and, as expected, less pronounced and less durable in older adults than in younger adults.

Clearly, a better theoretical understanding of brain plasticity in humans is a prerequisite for formulating hypotheses about the generality of training gains and for suggesting predictions about transfer gradients. This need for theory is especially pressing for cognitive functions, such as working memory and fluid intelligence, where mechanistic hypotheses of the processes associated with plastic change, including the potential transfer of this change to related tasks and abilities, are generally lacking. Instead, cognitive intervention studies typically probe plasticity in a rather improvised manner, guided by some general ideas about the likely site of cortical change along with some speculations about the potential for generalized behavioral improvements.

As others have noted, "[T]hose working in the field of [human] intervention should take stock in what is now known about neural plasticity" (Fox et al. 2010, p. 36). To make progress, research on human brain plasticity needs to incorporate findings from relevant animal models (Lövdén et al. 2013) and be informed by computational accounts of learning and habit formation (Dolan & Dayan 2013). The field requires process models that provide a theoretical template for delineating physiological manifestations of plastic episodes in the human brain (Bavelier et al. 2010, Gervain et al. 2013, Lövdén et al. 2012b, Steele & Zatorre 2018, Walhovd & Lövdén 2020, Zatorre 2013) instead of prematurely rushing to applications that have no theory to test.

Next, we review work on plasticity in animals and argue that this work, together with preliminary evidence in humans, allows for the formulation of a novel conceptual model that brings us closer to a process theory of human plasticity.

MECHANISMS OF PLASTICITY: INSIGHTS FROM ANIMAL MODELS

Spurred by new empirical methods, such as optogenetics and two-photon microscopy, recent research with animal models has made remarkable progress in identifying mechanisms that trigger, sustain, and terminate a plastic episode. In the following subsections, we review two strands of research based on animal models and related work on humans that together elucidate mechanisms of human brain plasticity: (*a*) the regulation of critical, or sensitive, periods and (*b*) plastic changes during skill learning. These bodies of work carry great potential for invigorating research on plasticity in humans and serve as the background for a novel model of plastic change that may facilitate a mechanistic turn in research on human plasticity.

Regulation of Critical Periods

Critical periods allow individuals to uniquely adapt their behaviors to social and physical aspects of their environments by shaping the organization of primary sensory areas in mammals and birds (Barkat et al. 2011, Wiesel & Hubel 1963). The timing of critical periods for distinct processing domains differs across developmental periods, and normal brain development is assumed to require temporal synchrony between intrinsic maturational programs and environmental input (Takesian & Hensch 2013).

In the midtwentieth century, it was discovered that the degree to which experience leads to lasting changes in brain and behavior varies markedly across ontogeny. Konrad Lorenz (1937) provided detailed descriptions of imprinting in nidifugous birds such as greylag geese. Torsten Wiesel and David Hubel (Wiesel & Hubel 1963, 1965) demonstrated that the nervous system is more likely to undergo lasting structural change through experience during specific developmental time periods, termed critical, in comparison to the time periods before or after. In a seminal series of studies on kittens, they sutured one of each kitten's eyes shortly after birth. When the deprived eye was reopened a few months later, it appeared normal, but most of the nerve cells in the visual cortex no longer responded to visual input from that eye. This blindness was found to reflect the elimination of connections to layer IV of the visual cortex. If occlusion extended beyond a

certain period, the typical pattern of ocular representation was not recovered when visual input was restored to both eyes (Wiesel & Hubel 1965). Remarkably, Hubel and Wiesel also found that the responses of the cells in the visual cortex remained unaltered compared with those of a normal cat if the procedure was carried out on an adult animal. Analogous observations have been made in humans who were born with cataracts and underwent cataract surgery at different ages (Guerreiro et al. 2016).

The discovery of critical periods led to a search for factors that influence their opening and closure. Animal models of critical period regulation indicate that the maturation of inhibitory interneurons drives critical period trajectories in primary sensory areas (Takesian & Hensch 2013). In this context, fast-spiking parvalbumin-expressing cells appear to play a critical role. These cells form a richly interconnected network, extend lateral inhibition by branching onto nearby pyramidal cells, influence action potential firing, and orchestrate rhythmic oscillations. Circuits of parvalbumin-expressing cells emerge at different times across different brain regions (Condé et al. 1996), which might contribute to the orderly progression of critical periods (Werker & Hensch 2015). Research has also shown that molecular triggers, which in turn may reflect experiential demands, can induce a plastic state, thereby opening a critical period (Putignano et al. 2007). The timing of the events that lead to these triggers is predicated on maturation, but experience is necessary as well. Once a plasticity window is open, experience or the lack thereof can lead to significant, and sometimes rapid, changes in wiring; thus, this is a time of both increased opportunity and vulnerability (Raz 2007, Walhovd & Lövdén 2020).

Molecular brakes on plasticity eventually consolidate the neural circuit from a plastic to a stable state. The closing of a critical period is an active process that helps preserve the changes that occurred during the plastic period. Brakes on plasticity include structural obstacles that physically prevent synaptic pruning and outgrowth, such as perineuronal nets (Lensjø et al. 2017, Sigal et al. 2019), or myelin-related signals including the Nogo receptor 1 and the immune gene receptor paired immunoglobulin-like receptor B (McGee et al. 2005, Syken et al. 2006).

In summary, molecular manipulations have confirmed that critical period timing itself is plastic and malleable. Of particular interest from a lifespan perspective, it appears that altering the excitatory/inhibitory (E/I) balance of local circuits from inhibition toward excitation might reopen windows of plasticity (Bavelier et al. 2010, Gervain et al. 2013, Hensch 2004, Takesian & Hensch 2013). As individuals mature, parvalbumin cells are gradually enwrapped by perineuronal nets, which act as plasticity brakes. Conversely, the experimental removal of perineuronal nets unlocks juvenile plasticity in rodents and is associated with decreased inhibition and increased gamma activity (Lensjø et al. 2017). Given that inhibitory parvalbumin cells and gamma oscillations are critical for the control of attention exerted by the prefrontal cortex (Fries et al. 2001, Kim et al. 2016), these findings point to a potential link between attentional mechanisms and plasticity regulation.

Plastic Changes During Skill Learning

A rich body of animal research describes neural changes that accompany the acquisition of novel skills (Hübener & Bonhoeffer 2014, Meyer et al. 2014). At least for motor learning, a reduction in cortical inhibitory tone appears to be critical for plasticity induction in the motor cortex (Chen et al. 2015, Donato et al. 2013, Peters et al. 2017). During motor skill learning or new sensory experiences, novel dendritic spines grow rapidly to form synapses in the sensory and motor cortices of mice (Hofer et al. 2009, Xu et al. 2009, Yang et al. 2009). It appears that dendrites play a crucial role in synaptic plasticity, as they generate many more spikes than the soma does and therefore qualify as a unit of neural computation (Moore et al. 2017). With continued training or experience,

the growth phase is followed by a slower process of stabilization of the new synapses and elimination of spines that had existed before training, almost returning the overall number of spines to pretraining levels, while performance on the trained task remains high. A small fraction of the new spines remain stable over a long period of time and might serve as a form of memory of the skill, rapidly becoming active as soon as the task is repeated (Hofer & Bonhoeffer 2010, Yang et al. 2009). The learning-induced and memory-supportive functions of dendritic spines are consistent with the hypothesis that the memory trace serving skilled performance has a localized and lasting substrate of rewired cortical circuitry (Fu et al. 2012, Fu & Zuo 2011, Guo et al. 2015, Hofer & Bonhoeffer 2010, Hofer et al. 2009, Holtmaat & Svoboda 2009, Poo et al. 2016, Tonegawa et al. 2015, Yang et al. 2009).

In line with these microscopic observations, macroscopic cortical changes during skill learning have been found to adhere to a pattern of expansion followed by renormalization (Molina-Luna et al. 2008, Pruitt et al. 2016, Reed et al. 2011). For example, rats trained to perform a skilled reaching task exhibited expanded cortical maps after three days of training (Molina-Luna et al. 2008). After eight days of training, however, expansions subsided, while behavioral performance remained stable. In a study on auditory cortex plasticity in rats, changes in global tonotopic representation during auditory operant conditioning followed a similar pattern (Takahashi et al. 2010). During early stages of training, tone-responsive areas in the core of the auditory cortex expanded; at later stages, when behavior was conditioned, both the core and belt cortices showed volume shrinkage. In another rodent study (Reed et al. 2011), nucleus basalis stimulation–tone pairing was accompanied by initial auditory cortical map extension. Subsequently, animals were trained in an auditory discrimination task, where improved discrimination learning was observed in animals with an expanded cortical map. Auditory cortex map expansion diminished over the following weeks but left tone discrimination performance unaffected. Thus, the expansion of the maps was related to the trajectory of learning but was not necessary for maintenance of the learned skill.

To bridge the gap between microscopic insights gained from animal studies and research on human plasticity, one needs to know whether processes associated with synapse formation and elimination can be captured on the macroscopic level with structural magnetic resonance imaging (MRI) methods. Changes in dendritic length, dendritic branching, and the number of dendritic spines per neuron (i.e., expansion and contraction of the neuropil) are likely to contribute to experience-dependent volumetric changes in gray matter (Cahill et al. 2015; Kassem et al. 2013; Lerch et al. 2017, 2011; Scholz et al. 2015a,b). In addition to neurons, various types of glial cells support brain functioning. They maintain ion homeostasis, regulate blood flow in response to neuronal activity, form myelin sheaths, and provide support and protection for neurons. Glial cells can increase in number, and they display several morphological changes in response to altered experience (Dong & Greenough 2004). Therefore, gliogenesis might, to some extent, also contribute to gray matter changes observable with MRI (Kassem et al. 2013, Zatorre et al. 2012).

Indeed, initial structural MRI evidence is at least consistent with the hypothesized expansion–renormalization pattern (Wenger et al. 2017a). Research has documented changes in human gray matter volume after a few months of training (Draganski et al. 2004, Draganski & May 2008, Lövdén et al. 2013) and has also indicated that such changes can emerge quite early during the learning process (Driemeyer et al. 2008, Taubert et al. 2016). In one study (Quallo et al. 2009), three adult macaque monkeys were scanned on multiple occasions before, during, and after learning how to use a rake to retrieve food. There were learning-related increases in task-relevant brain regions that also mapped onto the learning curves. Crucially, despite continued training, the observed increases in gray matter structure reversed as the monkeys' performance reached the asymptote. After training, the regional volume was still greater than before, but it was much smaller than the peak volume observed before asymptotic performance was reached.

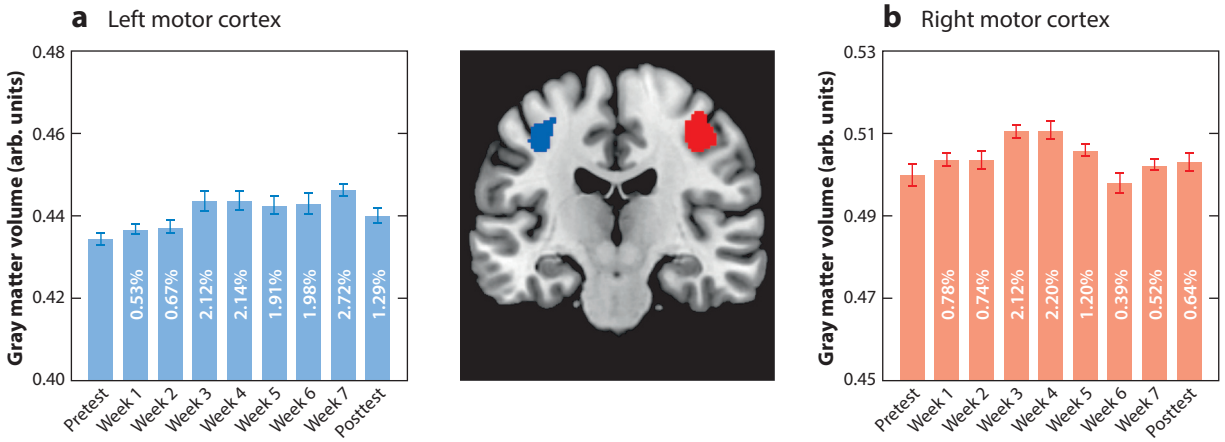

Figure 3

Evidence for nonmonotonic changes in gray matter volume during human skill learning. Fifteen right-handed adult participants practiced left-handed writing and drawing. Up to 18 T_1-weighted structural magnetic resonance images were acquired during the seven-week training period and were analyzed with voxel-based morphometry, yielding estimates of gray matter volume on the basis of the T_1-weighted signal. After four weeks, increases were observed in the estimates of gray matter volume in both (*a*) left and (*b*) right primary motor cortices relative to a control group; another three weeks later, these differences were no longer reliable. Time-series analyses showed that the estimates of gray matter volume in both primary motor cortices increased during the first four weeks and then partially renormalized, particularly in the right hemisphere, in the presence of continued practice and increasing task proficiency. The initial expansion of gray matter volumes might reflect exploration, whereas the partial renormalization observed thereafter might reflect selection and refinement. Figure adapted with permission from Wenger et al. (2017b).

More recently, Wenger et al. (2017b) acquired up to 18 T_1-weighted structural magnetic resonance images over a seven-week period, during which 15 right-handed adult participants practiced left-handed writing and drawing. The images were analyzed with voxel-based morphometry (VBM), yielding estimates of gray matter volume. After four weeks, increases were observed in the estimates of gray matter volume in both left and right primary motor cortices relative to a control group; however, three weeks later, these differences were no longer reliable. Time-series analyses showed that the estimates of gray matter volume in primary motor cortices increased during the first four weeks and then partially renormalized, particularly in the right hemisphere, in the presence of continued practice and increasing task proficiency (**Figure 3**).

In summary, synapse formation and elimination have been linked to learning-dependent changes in cortical function, and initial evidence in animals and humans suggests that these curvilinear changes might be discernible with structural MRI methods.

A DARWINIAN LEARNING MODEL OF PLASTICITY: EXPLORATION, SELECTION, AND REFINEMENT

To link the insights gained from animal studies on critical period regulation and skill learning more directly to research on human brain plasticity, we propose the ESR model of plastic change (see also Wenger et al. 2017a). The model is informed by Darwinian concepts of neural organization (Changeux & Dehaene 1989, Dhawale et al. 2017, Edelman 1987, Kilgard 2012, Makino et al. 2016), by the role of pruning in early ontogeny (Changeux & Dehaene 1989, Huttenlocher & Dabholkar 1997), and by theories of reinforcement learning (Daw et al. 2006, Dolan & Dayan 2013, Sharpe et al. 2019), which emphasize the importance of variability for learning (Dhawale et al. 2017, Garrett et al. 2013).

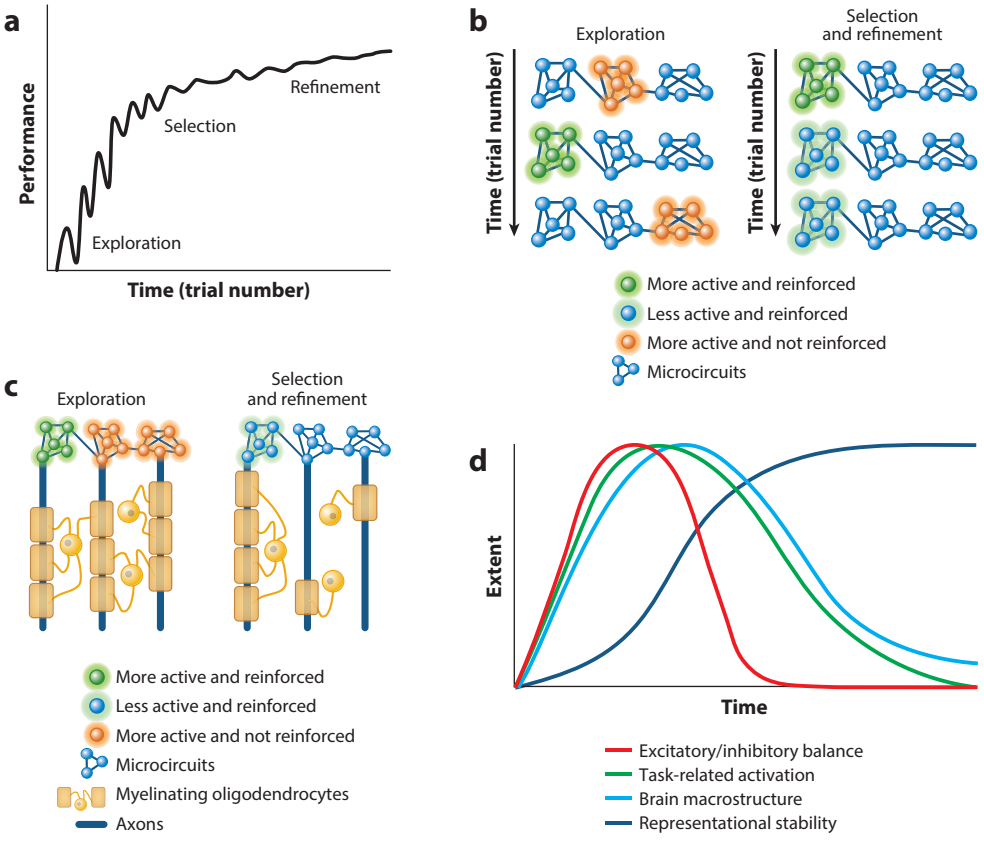

Figure 4

The exploration–selection–refinement (ESR) model of local plastic change. (*a*) According to the model, local plastic change proceeds in three phases that together form a learning cycle. During the initial stages of the exploration phase, when the brain probes available or generates new microcircuits that can execute the task, there is substantial trial-to-trial variability in (*a*) behavior and (*b*, *left*) patterns of neural activity (*c*, *left*). This broad and heightened level of activity induces structural change, such as the formation of new dendritic spines as well as other structural characteristics of the neuron, exemplified by myelination. As shown in panels *a* and *b* (*right*), through a process of reinforcement learning that is partly mediated by the neurotransmitter dopamine, the best-performing microcircuit is selected, and neural and behavioral variability starts to decrease. (*c*, *right*) In a subsequent refinement stage, processing in the selected microcircuit stabilizes through further structural refinement while novel structures of unselected microcircuits continue to retract. (*d*) At the macroscale of magnetic resonance imaging, the ESR model predicts curvilinear changes in brain metabolites, functional activation, and volume, in conjunction with a late-evolving monotonic increase in the self-similarity of neural activation patterns corresponding to a specific behavior or percept.

According to the ESR model, local plastic change proceeds in three phases that form a learning cycle (**Figure 4**). During the initial stages of the exploration phase, available neuronal microcircuits (neuronal ensembles) potentially capable of implementing the computations needed to execute a task are widely probed early in learning, and new circuits are formed. In the case of perceptual and motor skill learning, these circuits are located in primary and supplementary brain regions. During this phase, there is substantial trial-to-trial variability in patterns of neural activity in these regions as well as in behavior (Oby et al. 2019). Several sources may feed into this

variability, such as neural noise, trial-and-error exploration, and model-based planning, reflecting large-scale interactions with the frontostriatal brain system (Bassett et al. 2015, Sharpe et al. 2019). This phase shares at least conceptual similarities with the notion of exploration in decision theory, where it refers to choices that might not be expected to pay off immediately but, by increasing knowledge of the task space, might improve the prospects for earning rewards in the long run (Dayan & Daw 2008). Exploration in the sense of the ESR model is critical for acquiring new skills and might serve as a physiological substrate of exploration in the decision theoretical sense, given that the acquisition of any skill requires the acquisition of complex rules, which only pays off long term. Future research needs to implement and test these assumptions and hypotheses computationally.

The broad and heightened level of regional activity present during exploration results in structural change, such as the formation of new dendritic spines as well as other structural characteristics of the neuron (exemplified by myelination in **Figure 4*c***). Through mechanisms of reinforcement learning that are partly mediated by the neurotransmitter dopamine (Dolan & Dayan 2013), the best-performing microcircuit is selected, interaction between primary regions and the frontostriatal system is reduced, and neural variability in primary regions (and associated behavioral variability) starts to decrease (Dhawale et al. 2017). In a subsequent refinement stage, processing in the selected microcircuit is stabilized through further structural change, while novel structures of unselected (and, thus, no longer activated) microcircuits vanish.

Core Predictions of the Exploration–Selection–Refinement Model

At the macroscale of MRI, the ESR model predicts curvilinear changes in brain metabolites, functional activation, and volume, in conjunction with a late-evolving monotonic increase in the self-similarity of neural activation patterns. These four predictions of the ESR model are shown in **Figure 4*d*** and described below.

First, based on animal models of critical period regulation and skill acquisition, we expect that a plastic episode will typically be triggered, among other things, by a transient shift in E/I balance toward excitation. Recent methodological advances in functional magnetic resonance spectroscopy (MRS) at high field strength (Stanley & Raz 2018) might enable researchers to test this proposition by imaging transient changes in neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate in the course of skill acquisition in humans.

Second, we predict that the probing of new microcircuits that compete for control over behavior will lead to an increase in neural activity, resulting in local strengthening of the blood oxygen level–dependent (BOLD) signal in functional MRI (fMRI). During the phases of microcircuit selection and refinement, the BOLD signal will decrease gain, possibly back to baseline levels. Such a curvilinear pattern has indeed been observed in the human visual cortex during visual discrimination training (Yotsumoto et al. 2008) and motor skill learning (Ma et al. 2010). More generally, motor sequence learning is associated with increasing motor system activity in the early stages of learning, followed by a reduction in activity during execution of highly practiced motor behavior (Bassett et al. 2015, Wymbs & Grafton 2015).

Third, we predict that the ESR cycle will result in a local expansion of brain macrostructure followed by partial renormalization. These macroscopic changes are likely to reflect a mixture of processes, such as changes in dendritic length, in dendritic branching, and in the number of dendritic spines per neuron, but also in myelination and gliogenesis, which together are discernible as gray matter changes with structural MRI methods.

Fourth, the ESR model motivates predictions regarding the self-similarity of neural activity in the course of plastic change. During the exploration phase, many neural microcircuits compete for

control of behavior. Therefore, neural activity should be high, whereas trial-to-trial self-similarity of activity patterns should be low, reflecting the fleeting nature of brain–behavior mappings. During the selection phase, the amount of activity should decrease, whereas the self-similarity of activation patterns from trial to trial should increase, as behavior is increasingly dominated by a small number of microcircuits. This process might continue during the final phase of refinement, when the neural representation of the newly acquired behavior becomes sparse and stable (Gdalyahu et al. 2012). Research with fMRI in humans partially supports these predictions, showing that motor skill learning results in patterns of functional activity that become more dissimilar among trained sequences of movements and that trained sequences generally become more dissimilar to untrained sequences of movement, too (Wiestler & Diedrichsen 2013). If these changes were accompanied by increases in self-similarity from trial to trial, then this would suggest that practice leads to dedicated neuronal ensembles for specific sequences of movements. Likewise, we hypothesize that plastic change in the perceptual domain would increase the self-similarity of the cortical representations of identical percepts (e.g., tones of identical timbre and pitch) and the dissimilarity of the cortical representations for different percepts (e.g., tones that differ in timbre or pitch).

Research Design Implications of the Exploration–Selection–Refinement Model

The ESR model has research design implications for cognitive training studies. In order to make better contact with neuroscience, it is imperative that research on human plasticity move away from the pretest–posttest design, which implicitly equates plasticity with monotonic growth, toward research designs that can capture nonmonotonic structural changes in the context of neurochemical changes, functional reorganization, connectivity changes, representational changes, and increasing behavioral proficiency. Only research designs with multiple observations in the course of plastic change can detect tissue expansion followed by renormalization and investigate whether exploration, selection, and refinement mechanisms contribute to this pattern. Research designs with one structural imaging session at pretest and another at posttest cannot chart the temporal progression and underlying dynamics of plastic change. The posttest may hit the peak of tissue expansion if it happens to take place in the middle of skill learning when asymptotic levels of behavioral proficiency have not yet been reached. Conversely, the posttest may suggest absence of structural change if it happens to take place before or after this peak. In addition, individuals may differ in the amount of experience they need in order to go through the phases of exploration, selection, and refinement. As a result, a fixed posttest session may capture the peak of tissue expansion in some individuals, whereas others might not yet have attained that peak or might have moved beyond the peak. Therefore, we recommend the use of research designs that do justice to plasticity as a nonmonotonic, dynamic process that might differ in rate of progression between individuals and age groups. This requires the administration of multiple sessions of structural imaging that cover the early, middle, and late phases of behavioral change, ideally augmented by multiple sessions of fMRI and functional MRS.

Furthermore, the ESR model emphasizes the need to move toward mechanistically more interpretable imaging techniques. For instance, structural changes in gray matter during skill learning have typically been assessed using VBM. While repeated VBM measurements yield an estimate of overall volume change, they do not provide a solid basis for inferring the nature of these changes. To the extent that plastic changes are accompanied by local changes in myelination, myelinated cortical thickness imaging and related techniques (Rowley et al. 2015, Waehnert et al. 2014) might have better specificity than VBM does to observe the nature of the unfolding structural changes. Similarly, repeated functional MRS imaging (Stanley & Raz 2018) helps track changes in metabolites that reflect changes in E/I balance, and electroencephalographic or magnetoencephalographic assessments can help clarify the role of local oscillatory activity in the

gamma frequency range during different phases of the plasticity cycle. Also, variants of representational similarity analysis (Kriegeskorte & Kievit 2013) and related multivariate pattern analyses can be used to test the prediction that neural activation patterns become less variable from trial to trial as behavior approaches asymptotic levels of performance.

Finally, to narrow the gap between human research and animal models, human training studies should match the current emphasis on higher cognitive functions with an equal emphasis on paradigms that target plasticity of the sensory and motor cortices (Doyon & Benali 2005, Lerch et al. 2017). Difficulties of cross-species comparisons notwithstanding, a concerted research effort would involve an animal lab using high-resolution methods (e.g., optogenetics and two-photon microscopy), an animal lab and a human lab each using MRI methods, and all labs targeting an equivalent motor or sensory task. Such a research effort could directly test the predictions of the ESR model, and would help gauge the mechanistic interpretability of human brain imaging techniques.

PUTTING THE EXPLORATION–SELECTION–REFINEMENT MODEL INTO A LIFESPAN CONTEXT

In the following subsections, we link the ESR model to a broader set of research questions that speak to the contributions of plasticity to individual differences in lifespan development.

The Changing Contexts of Local Plastic Change

The emphasis of the ESR model is on a three-partite sequence of local plastic changes and how this sequence unfolds in interaction with other task-relevant brain areas. Little is known about the ways in which age-related changes and between-person differences in large-scale network topography affect the context for local plastic change (Ziegler et al. 2019). Cognitive development from childhood to adulthood is accompanied by profound changes in structural and functional connectivity, presumably associated with declines in general neural synchronizability and increases in controllability (Tang et al. 2017, Uhlhaas et al. 2009). Thus, the cerebral context for learning a new skill alters with age, and these changes may affect plasticity at the local level. In particular, the maturation of the parietal and prefrontal cortices during childhood and adolescence leads to an increase in top-down strategic control over perception and action during childhood (Church et al. 2017, Decker et al. 2016). This increase in control may help specify the supply–demand mismatch and hence direct attention to specific aspects of behavior that need plastic change. However, this increase could also sometimes hinder plastic change by excessive strategic guidance of local exploration–selection dynamics. For instance, while directing attention toward the to-be-acquired skill may generally be helpful, overly precise knowledge about what should be done to learn it may lead to an overinstruction of local circuits that hinders local plastic change. Age-comparative studies of skill learning are needed to probe this claim.

Plasticity Beyond Primary Cortices

Despite some progress (Dahlin et al. 2008, Mackey et al. 2013, Vendetti & Bunge 2014), the physiological substrates that underlie attempts to alter cognitive abilities such as working memory and fluid intelligence through behavioral interventions are generally not known. For example, the relative importance of local plastic change in the frontal cortices for interventions targeting cognitive abilities such as working memory is not well understood. It is unclear whether local plastic change observed in the primary sensory and motor cortices in the context of critical periods or skill learning offers a viable analogy to the role of the prefrontal cortex in the context of cognitive abilities.

Can we target a cognitive function, such as efficient switching between task sets, and identify a cortical area that shows signs of exploration, selection, and refinement as this function improves? Or is improvement of cognitive abilities 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, in the absence of any major structural change? How do age-graded changes in maturation and senescence alter the relative contribution of plasticity and flexibility? The answers to these questions are not known at present.

One might speculate that plastic change in cognitive abilities, if it occurs, requires a mixture of local plastic change (e.g., akin to cortical map extension in the primary cortices) and more distributed changes such as increased myelination of relevant white matter tracts in the service of improved network reorganization (Fields & Dutta 2019, Forstmann et al. 2010, Fries 2015, Kaller et al. 2017). In this context, it is worth exploring whether mechanisms serving top-down control might help trigger local plasticity during skill learning. In particular, oscillatory activity in the gamma range, which is required for cognitive control (Kim et al. 2016), might contribute to perineuronal net erosion in local circuits (Lensjø et al. 2017). This property of gamma activity might help explain how windows of plasticity can be opened in an attention-driven, circumscribed, and adaptive manner in the adult brain.

The Memory of Plasticity

Animal models have shown how experiences triggering plastic change leave a lasting trace in neocortical and hippocampal circuits (Hayashi-Takagi et al. 2015, Hofer & Bonhoeffer 2010, Hofer et al. 2009, Hübener & Bonhoeffer 2010, Meyer et al. 2014, Queenan et al. 2017, Tonegawa et al. 2015, Yang et al. 2009). For instance, Yang et al. (2009) observed spine formation and elimination in layer V pyramidal neurons of the motor cortex in rodents during motor skill learning. Importantly, a small fraction of new spines was preserved and provided a structural substrate for memory retention throughout the animals' lifetime. Thus, plastic changes during skill learning form lifelong memories stored in stably connected neural networks. Accordingly, when a previously acquired skill is reactivated rather than learned anew, the ESR sequence should be greatly attenuated and accelerated.

Human evidence for select domains of functioning, such as musical skills, indicates that experience-dependent structural brain changes tend to be more durable when they occur earlier during ontogeny (Elbert et al. 1995), suggesting that the mechanisms protecting the engram against loss through metabolic turnover might be more active in children than in adults (Meyer et al. 2014). On the basis of these considerations, we propose that children might show a greater reduction in the ESR pattern compared with the original plastic episode than adults when a previously acquired skill is reactivated at a later point in time. We note that this expectation is difficult to test empirically, as the relevant local microcircuits are modulated by a system that has undergone massive changes in large-scale connectivity.

Exploiting the Exploration Phase of the Plasticity Cycle

Cognitive intervention studies often bear the promise that the effects of training generalize beyond the trained task. From the perspective of the ESR model, it would be surprising if microcircuits that are recruited to cope with a particular task would be easily amenable to other tasks from the same or a related functional domain. In other words, without further amendment, the ESR model does not provide a strong basis for predicting transfer, unless transfer is taken to mean that identical behavior is executed in a different context. Given that transfer effects are generally small

or absent unless there is direct overlap between elements of the acquired skill and elements of a different skill (Thorndike 1898), this feature of the model does not appear to be problematic.

However, the ESR model is consistent with another proposition that might carry some applied value. According to this proposition, the potential for extending the intervention to other, related skills is particularly high during the exploration phase of the plasticity cycle, when numerous neural microcircuits are competing for control over behavior. During exploration, individuals probe the consequences of various actions and register and update their values (Daw et al. 2006, Dolan & Dayan 2013, Sharpe et al. 2019). Introducing a wider array of additional tasks during this phase of the ESR cycle that partially overlap in processing demands with the original task might trigger a branching-off process of skill differentiation and broadening, in the sense that some of the microcircuits that are being probed, and thus initially strengthened, for the control of the original task are recruited by the newly introduced tasks. This notion of skill broadening resonates well with pedagogical considerations of effective instruction (Geary 2006).

Therefore, we predict that the exploration phase of the ESR cycle is more germane to skill broadening than the selection and refinement stages, when the neural representation of the newly acquired skill stabilizes. This prediction is in line with principles of reinforcement learning, which emphasize the importance of variability for learning and generalization (Dhawale et al. 2017, Garrett et al. 2013; see also Skinner 1981, Thorndike 1898). It also is consistent with the aforementioned results reported by Schmiedek et al. (2010), who used a training regime in which 12 cognitive tasks from three ability domains were practiced for approximately 100 days and observed transfer at the level of cognitive abilities.

Cycles of Plasticity

Skill broadening speaks to the synchronous acquisition of multiple related skills during the exploration phase of a given ESR cycle. Diachronically, it is likely that real-life complex skills are constructed in the course of multiple cycles of plasticity (Donner & Hardy 2015), some of which may partly occur in parallel. Learning to play a musical instrument (Elbert et al. 1995) or to speak a new language (Werker & Hensch 2015) consists of a series of sequentially ordered and hierarchically nested subskills. Relative to baseline, the articulated succession of plasticity cycles related to these subskills might escape macrostructural renormalization and result in permanently larger task-relevant brain structures in comparison to individuals who have not had the same experiences. This observation might help explain why 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 performance on tests of executive functions (Yuan & Raz 2014). Apparently, both neural code efficiency and brain size determine an individual's effective functional cerebral space (Kinsbourne & Hicks 1978).

Clearly, the recursive relations between brain size and processing efficiency, and the contribution of plasticity to both, are not well understood. Individual differences in the number and type of plasticity cycles might help explain individual differences in brain size, structure, and behavior (Tucker-Drob 2017). Studies with dense brain imaging data on the acquisition of complex real-life skills are needed to shed light on these associations. Ideally, individuals participating in these studies should be drawn from longitudinal panels to link mechanisms of skill learning to individual differences in developmental trajectories before and after skill learning. In adulthood, and especially in old age, cognitive interventions may trigger positive deviations from the modal path of cognitive aging by preventing the structural decline that would have occurred otherwise. Thus, with advancing adult age, plasticity might increasingly serve the function of maintaining

behaviorally relevant neural substrates (Lindenberger et al. 2013, Nyberg & Lindenberger 2020, Nyberg et al. 2012).

Gene–Environment Interplay

To elucidate individual differences in behavioral development, the ESR model needs to make contact with genetic and environmental sources of variation (Beam & Turkheimer 2013, Freund et al. 2013). The prevailing view has long been that expert levels of performance almost exclusively reflect the outcome of long-term deliberate practice (Ericsson & Simon 1993). In contrast to this assumption, meta-analyses have found that practice uniquely accounts for only a modest proportion of variance in performance (for a summary, see Ullén et al. 2016). In addition, recent studies have identified antecedents of expert performance. For instance, working memory and cognitive ability contribute to individual differences in musical expertise (Ullén et al. 2016).

Gene–environment interplay, which is essential for human variation in general (Beam & Turkheimer 2013, Plomin et al. 2016), also plays a decisive role in plasticity and, hence, skill learning. In the domain of music, for instance, genetic influences predict individual differences in music practice and broadly shape the covariation among practice, performance, achievement, personality, and interests (Butkovíc et al. 2015, Mosing et al. 2014, Ullén et al. 2016). These findings are consistent with the notion of gene–environment covariation, that is, with the proposition that people tend to choose, or are selected into, environments that complement their heredity (Beam & Turkheimer 2013, Plomin et al. 2016, Scarr & McCartney 1983, Tucker-Drob 2017). In particular, Tucker-Drob (2017) recently suggested that genetic factors might drive the type, frequency, consistency, and repetition of exposures to trait-relevant experiences. Thus, future research needs to address whether and how individual differences in exploration, selection, and refinement in the course of skill learning are related to genetic and epigenetic variation. For instance, individual differences in dopamine-related genes may affect plasticity by regulating the range of exploration (Bellander et al. 2015).

CONCLUDING REMARKS

In this review, we have sought to promote a general conceptual framework that places research on human brain plasticity in the context of animal models, tenets from lifespan psychology, and theories of learning. To foster this theoretical context, we have introduced the ESR model of plastic change, which makes a number of mechanistically grounded predictions that can be tested in humans (**Figure 4**). In doing so, we have painted topics and findings with a broad brush, at the cost of leaving out important details. For instance, we have not discussed how circadian rhythms contribute to developmental differences in plasticity (Smarr et al. 2014). Similarly, we have not specifically addressed hippocampal plasticity, despite its prominent role throughout ontogeny (Freund et al. 2013, Keresztes et al. 2018, Snyder 2019). Also, due to our focus on local mechanisms, the contribution of large-scale circuits (Garrett et al. 2018, Sharpe et al. 2019, Tang et al. 2017) to lifespan changes in plasticity has received little attention. Finally, we have not dwelt on the plasticity challenges associated with specific developmental periods, such as adolescence (Gelinas et al. 2018, Patel et al. 2019).

From both scientific and societal perspectives, plasticity is a precious phenomenon (Freund et al. 2013; Kühn & Lindenberger 2016; Lindenberger 2014, 2018). Scientifically, triggering episodes of plastic change experimentally offers the promise to observe the operation and proximal consequences of the learning mechanisms that shape development. From the perspective of societal evolution, intervention studies explore the range of possible development, or what could

be possible in principle if conditions were different (Baltes et al. 2006, Gottlieb 1998). The resulting knowledge about the plasticity of developmental trajectories is essential for improving human welfare. Therefore, the concept of a plastic human mind has attracted much scientific and public attention. The so-called brain-training industry nurtures the hopes of many by promoting the idea that playing games will make them smarter, more alert, and able to learn faster and better. Instead of making premature promises about real-life benefits, which ultimately bring disappointment and undermine the credibility of science, we need to strive toward an understanding of human plasticity that is informed by principles of brain development, large-scale theories of the brain, and neural accounts of critical period regulation and skill learning. We hope that the ESR model of plastic change is a productive contribution toward this goal.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

U.L. expresses his gratitude to the Max Planck Society for decades of funding support and scientific freedom. M.L. acknowledges funding support from the European Research Council (ERC) under the European Union's Seventh Framework Program (FP7/2007–2013)/ERC grant agreement 617280-REBOOT, and a grant from the Swedish Research Council (446-2013-7189). The authors thank Julia Delius, Benjamin Garzón, Simone Kühn, and Elisabeth Wenger for helpful discussions and Tobias Bonhoeffer, Peter Dayan, Julia Delius, and Naftali Raz for comments on an earlier version of this article.

LITERATURE CITED

Bäckman L, Lindenberger U, Li S-C, Nyberg L. 2010. Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. *Neurosci. Biobehav. Rev.* 34:670–77

Baltes PB. 1997. On the incomplete architecture of human ontogeny: selection, optimization and compensation as foundation of developmental theory. *Am. Psychol.* 52:366–80

Baltes PB, Kliegl R. 1992. Further testing of limits of cognitive plasticity: negative age differences in a mnemonic skill are robust. *Dev. Psychol.* 28:121–25

Baltes PB, Kliegl R, Dittmann-Kohli F. 1988. On the locus of training gains in research on the plasticity of fluid intelligence in old age. *J. Educ. Psychol.* 80:392–400

Baltes PB, Lindenberger U, Staudinger UM. 2006. Life span theory in developmental psychology. In *Handbook of Child Psychology: Theoretical Models of Human Development*, ed. W Damon, RM Lerner, pp. 569–664. New York: Wiley

Barkat TR, Polley DB, Hensch TK. 2011. A critical period for auditory thalamocortical connectivity. *Nat. Neurosci.* 14:1189–94

Bassett DS, Yang M, Wymbs NF, Grafton ST. 2015. Learning-induced autonomy of sensorimotor systems. *Nat. Neurosci.* 18:744–51

Bavelier D, Levi DM, Li RW, Dan Y, Hensch TK. 2010. Removing brakes on adult brain plasticity: from molecular to behavioral interventions. *J. Neurosci.* 30:14964–71

Beam CR, Turkheimer E. 2013. Phenotype–environment correlations in longitudinal twin models. *Dev. Psychopathol.* 25:7–16

Bediou B, Adams DM, Mayer RE, Tipton E, Green CS, Bavelier D. 2018. Meta-analysis of action video game impact on perceptual, attentional, and cognitive skills. *Psychol. Bull.* 144:77–110

Bellander M, Bäckman L, Liu T, Schjeide B-MM, Bertram L, et al. 2015. Lower baseline performance but greater plasticity of working memory for carriers of the val allele of the COMT Val^{158}Met polymorphism. *Neuropsychology* 29: 247–54

Blagosklonny MV, Hall MN. 2009. Growth and aging: a common molecular mechanism. *Aging* 1:357–62

Blair C, Kuzawa CW, Willoughby MT. 2020. The development of executive function in early childhood is inversely related to change in body mass index: evidence for an energetic tradeoff? *Dev. Sci.* 23:e12860

Bourgeois JP. 1997. Synaptogenesis, heterochrony and epigenesis in the mammalian neocortex. *Acta Paediatr.* 422:27–33

Brandmaier AM, von Oertzen T, Ghisletta P, Lindenberger U, Hertzog C. 2018a. Precision, reliability and effect size of slope variance in latent growth curve models: implications for statistical power analysis. *Front. Psychol.* 9:294

Brandmaier AM, Wenger E, Bodammer NC, Kühn S, Raz N, Lindenberger U. 2018b. Assessing reliability in neuroimaging research through intra-class effect decomposition (ICED). *eLife* 7:e35718

Brehmer Y, Li S-C, Müller V, Oertzen TV, Lindenberger U. 2007. Memory plasticity across the life span: uncovering children's latent potential. *Dev. Psychol.* 43:465–78

Brehmer Y, Li S-C, Straube B, Stoll G, Oertzen TV, et al. 2008. Comparing memory skill maintenance across the lifespan: preservation in adults, increase in children. *Psychol. Aging* 23:227–38

Butkovíc A, Ullén F, Mosing MA. 2015. Personality and related traits as predictors of music practice: underlying environmental and genetic influences. *Personal. Individ. Differ.* 74:133–38

Cabeza R, Albert M, Belleville S, Craik FIM, Duarte A, et al. 2018. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat. Rev. Neurosci.* 19:701–10

Cahill LS, Steadman PE, Jones CE, Laliberté CL, Dazai J, et al. 2015. MRI-detectable changes in mouse brain structure induced by voluntary exercise. *NeuroImage* 113:175–83

Changeux J-P, Dehaene S. 1989. Neuronal models of cognitive functions. *Cognition* 33:63–109

Chen SX, Kim AN, Peters AJ, Komiyama T. 2015. Subtype-specific plasticity of inhibitory circuits in motor cortex during motor learning. *Nat. Neurosci.* 18:1109–15

Church JA, Bunge SA, Petersen SE, Schlaggar BL. 2017. Preparatory engagement of cognitive control networks increases late in childhood. *Cereb. Cortex* 27:2139–53

Clopath C, Bonhoeffer T, Hübener M, Rose T. 2017. Variance and invariance of neuronal long-term representations. *Philos. Trans. R. Soc. B* 372:20160161

Condé F, Lund JS, Lewis DA. 1996. The hierarchical development of monkey visual cortical regions as revealed by the maturation of parvalbumin-immunoreactive neurons. *Brain Res. Dev.* 96:261–76

Dahlin E, Stigsdotter Neely A, Larsson A, Bäckman L, Nyberg L. 2008. Transfer of learning after updating training mediated by the striatum. *Science* 320:1510–12

Daw ND, O'Doherty JP, Dayan P, Seymour B, Dolan RJ. 2006. Cortical substrates for exploratory decisions in humans. *Nature* 441:876–79

Dayan P, Daw ND. 2008. Decision theory, reinforcement learning, and the brain. *Cogn. Affect. Behav. Neurosci.* 8:429–53

Decker JH, Otto AR, Daw ND, Hartley CA. 2016. From creatures of habit to goal-directed learners: tracking the developmental emergence of model-based reinforcement learning. *Psychol. Sci.* 27:848–58

Dhawale AK, Smith MA, Ölveczky BP. 2017. The role of variability in motor learning. *Annu. Rev. Neurosci.* 40:479–98

Dolan RJ, Dayan P. 2013. Goals and habits in the brain. *Neuron* 80:312–25

Donato F, Rompani SB, Caroni P. 2013. Parvalbumin-expressing basket-cell network plasticity induced by experience regulates adult learning. *Nature* 504:272–76

Dong WK, Greenough WT. 2004. Plasticity of nonneuronal brain tissue: roles in developmental disorders. *Ment. Retard. Dev. Disabil. Res. Rev.* 10:85–90

Donner Y, Hardy JL. 2015. Piecewise power laws in individual learning curves. *Psychon. Bull. Rev.* 22:1308–19

Doyon J, Benali H. 2005. Reorganization and plasticity in the adult brain during learning of motor skills. *Curr. Opin. Neurobiol.* 15:161–67

Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. 2004. Changes in grey matter induced by training. *Nature* 427:311–12
Draganski B, May A. 2008. Training-induced structural changes in the adult human brain. *Behav. Brain Res.* 192:137–42
Driemeyer J, Boyke J, Gaser C, Buchel C, May A. 2008. Changes in gray matter induced by learning—revisited. *PLOS ONE* 3:e2669
Edelman GM. 1987. *Neural Darwinism: The Theory of Neuronal Group Selection*. New York: Basic
Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. 1995. Increased cortical representation of the fingers of the left hand in string players. *Science* 270:305–7
Elman JL, Bates EA, Johnson MH, Karmiloff-Smith A, Parisi D, Plunkett K. 1996. *Rethinking Innateness: A Connectionist Perspective on Development*. Cambridge, MA: MIT Press
Ericsson KA, Simon HA. 1993. *Protocol Analysis: Verbal Reports as Data*. Cambridge, MA: Bradford/MIT Press. Revis. ed.
Fields RD, Dutta DJ. 2019. Treadmilling model for plasticity of the myelin sheath. *Trends Neurosci*. 42:443–47
Forstmann BU, Anwander A, Schäfer A, Neumann J, Brown S, et al. 2010. Cortico-striatal connections predict control over speed and accuracy in perceptual decision making. *PNAS* 107:15916–20
Fox SE, Levitt P, Nelson CA. 2010. How the timing and quality of early experiences influence the development of brain architecture. *Child Dev*. 81:28–40
Freund J, Brandmaier AM, Lewejohann L, Kirste I, Kritzler M, et al. 2013. Emergence of individuality in genetically identical mice. *Science* 340:756–59
Fries P. 2015. Rhythms for cognition: communication through coherence. *Neuron* 88:220–35
Fries P, Reynolds JH, Rorie AE, Desimone R. 2001. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 291:1560–63
Fu M, Yu X, Lu J, Zuo Y. 2012. Repetitive motor learning induces coordinated formation of clustered dendritic spines in vivo. *Nature* 483:92–95
Fu M, Zuo Y. 2011. Experience-dependent structural plasticity in the cortex. *Trends Neurosci*. 34:177–87
Garrett DD, Epp SM, Perry A, Lindenberger U. 2018. Local temporal variability reflects functional integration in the human brain. *NeuroImage* 183:776–87
Garrett DD, Samanez-Larkin GR, MacDonald SWS, Lindenberger U, McIntosh AR, Grady CL. 2013. Moment-to-moment brain signal variability: a next frontier in human brain mapping? *Neurosci. Biobehav. Rev.* 37:610–24
Gdalyahu A, Tring E, Polack P-O, Gruver R, Golshani P, et al. 2012. Associative fear learning enhances sparse network coding in primary sensory cortex. *Neuron* 75:121–32
Geary DC. 2006. Development of mathematical understanding. In *Handbook of Child Psychology: Cognition, Perception, and Language*, ed. D Kuhn, RS Siegler, pp. 777–810. Hoboken, NJ: Wiley
Gelinas JN, Baillet S, Bertrand O, Galván A, Kolling T, et al. 2018. Late adolescence: critical transitions into adulthood. In *Emergent Brain Dynamics: Prebirth to Adolescence*, ed. AA Benasich, U Ribary, pp. 243–64. Cambridge, MA: MIT Press
Gervain J, Vines BW, Chen LM, Seo RJ, Hensch TK, et al. 2013. Valproate reopens critical-period learning of absolute pitch. *Front. Syst. Neurosci.* 7:102
Gordon EM, Laumann TO, Gilmore AW, Newbold DJ, Greene DJ, et al. 2017. Precision functional mapping of individual human brains. *Neuron* 95:791–807
Gottlieb G. 1998. Normally occurring environmental and behavioral influences on gene activity: from central dogma to probabilistic epigenesis. *Psychol. Rev.* 105:792–802
Greenough WT, Black JE, Wallace CS. 1987. Experience and brain development. *Child Dev*. 58:539–59
Guerreiro MJS, Putzar L, Röder B. 2016. Persisting cross-modal changes in sight-recovery individuals modulate visual perception. *Curr. Biol.* 26:3096–100
Guo J-Z, Graves AR, Guo WW, Zheng J, Lee A, et al. 2015. Cortex commands the performance of skilled movement. *eLife* 4:e10774
Hayashi-Takagi A, Yagishita S, Nakamura M, Shirai F, Wu YI, et al. 2015. Labelling and optical erasure of synaptic memory traces in the motor cortex. *Nature* 525:333–35

Hensch TK. 2004. Critical period regulation. *Annu. Rev. Neurosci.* 27:549–79
Hilgard J, Sala G, Boot WR, Simons DJ. 2019. Overestimation of action-game training effects: publication bias and salami slicing. *Collabra Psychol.* 5:30
Hofer SB, Bonhoeffer T. 2010. Dendritic spines: the stuff that memories are made of? *Curr. Biol.* 20:R157–59
Hofer SB, Mrsic-Flogel TD, Bonhoeffer T, Hübener M. 2009. Experience leaves a lasting structural trace in cortical circuits. *Nature* 457:313–18
Holtmaat A, Svoboda K. 2009. Experience-dependent structural synaptic plasticity in the mammalian brain. *Nat. Rev. Neurosci.* 10:647–58
Hübener M, Bonhoeffer T. 2010. Searching for engrams. *Neuron* 67:363–71
Hübener M, Bonhoeffer T. 2014. Neuronal plasticity: beyond the critical period. *Cell* 159:727–37
Huttenlocher PR, Dabholkar AS. 1997. Regional differences in synaptogenesis in human cerebral cortex. *J. Comp. Neurol.* 387:167–78
Kaller MS, Lazari A, Blanco-Duque C, Sampaio-Baptista C, Johansen-Berg H. 2017. Myelin plasticity and behaviour—connecting the dots. *Curr. Opin. Neurobiol.* 47:86–92
Karch JD, Filevich E, Wenger E, Lisofsky N, Becker M, et al. 2019. Identifying predictors of within-person variance in MRI-based brain volume estimates. *NeuroImage* 200:575–89
Kassem MS, Lagopoulos J, Stait-Gardner T, Price WS, Chohan TW, et al. 2013. Stress-induced grey matter loss determined by MRI is primarily due to loss of dendrites and their synapses. *Mol. Neurobiol.* 47:645–61
Keresztes A, Ngo CT, Lindenberger U, Werkle-Bergner M, Newcombe NS. 2018. Hippocampal maturation drives memory from generalization to specificity. *Trends Cogn. Sci.* 22:676–86
Kievit RA, Brandmaier AM, Ziegler G, van Harmelen AL, de Mooij SMM, et al. 2018. Developmental cognitive neuroscience using latent change score models: a tutorial and applications. *Dev. Cogn. Neurosci.* 33:99–117
Kilgard MP. 2012. Harnessing plasticity to understand learning and treat disease. *Trends Neurosci.* 36:715–22
Kim H, Ahrlund-Richter S, Wang X, Deisseroth K, Carlen M. 2016. Prefrontal parvalbumin neurons in control of attention. *Cell* 164:208–18
Kinsbourne M, Hicks RE. 1978. Functional cerebral space: a model for overflow, transfer and interference effects in human performance. A tutorial review. In *Attention and Performance*, ed. J Requin, pp. 345–62. Hillsdale, NJ: Erlbaum
Kirkwood TBL. 2005. Understanding the odd science of aging. *Cell* 120:437–47
Knudsen EI. 1998. Capacity for plasticity in the adult owl auditory system expanded by juvenile experience. *Science* 279:1531–33
Koen JD, Rugg MD. 2019. Neural dedifferentiation in the aging brain. *Trends Cogn. Sci.* 23:547–59
Krakauer JW, Ghazanfar AA, Gomez-Marin A, MacIver MA, Poeppel D. 2017. Neuroscience needs behavior: correcting a reductionist bias. *Neuron* 93:480–90
Kriegeskorte N, Kievit RA. 2013. Representational geometry: integrating cognition, computation, and the brain. *Trends Cogn. Sci.* 17:401–12
Kühn S, Gleich T, Lorenz RC, Lindenberger U, Gallinat J. 2014. Playing Super Mario induces structural brain plasticity: grey matter changes resulting from training with a commercial video game. *Mol. Psychiatry* 19:265–71
Kühn S, Lindenberger U. 2016. Research on human plasticity in adulthood: a lifespan agenda. In *Handbook of the Psychology of Aging*, ed. KW Schaie, SL Willis, pp. 105–23. San Diego, CA: Elsevier. 8th ed.
Kühn S, Schmiedek F, Noack H, Wenger E, Bodammer NC, et al. 2013. The dynamics of change in striatal activity following updating training. *Hum. Brain Mapp.* 34:1530–41
Kuzawa CW, Chugani HT, Grossman LI, Lipovich L, Muzik O, et al. 2014. Metabolic costs and evolutionary implications of human brain development. *PNAS* 111:13010–15
Lensjø KK, Lepperod ME, Dick G, Hafting T, Fyhn M. 2017. Removal of perineuronal nets unlocks juvenile plasticity through network mechanisms of decreased inhibition and increased gamma activity. *J. Neurosci.* 37:1269–83
Lerch JP, van der Kouwe AJW, Raznahan A, Paus T, Johansen-Berg H, et al. 2017. Studying neuroanatomy using MRI. *Nat. Neurosci.* 20:314–26

Lerch JP, Yiu AP, Martinez-Canabal A, Pekar T, Bohbot VD, et al. 2011. Maze training in mice induces MRI-detectable brain shape changes specific to the type of learning. *NeuroImage* 54:2086–95
Li S-C. 2003. Biocultural orchestration of developmental plasticity across levels: the interplay of biology and culture in shaping the mind and behavior across the life span. *Psychol. Bull.* 129:171–94
Lindenberger U. 2014. Human cognitive aging: corriger la fortune? *Science* 346:572–78
Lindenberger U. 2018. Plasticity beyond early development: hypotheses and questions. In *Emergent Brain Dynamics: Prebirth to Adolescence*, ed. AA Benasich, U Ribary, pp. 207–23. Cambridge, MA: MIT Press
Lindenberger U, Burzynska AZ, Nagel IE. 2013. Heterogeneity in frontal-lobe aging. In *Principles of Frontal Lobe Functions*, ed. DT Stuss, RT Knight, pp. 609–27. New York: Oxford Univ. Press
Lindenberger U, Li S-C, Bäckman L. 2006. Delineating brain–behavior mappings across the lifespan: substantive and methodological advances in developmental neuroscience. *Neurosci. Biobehav. Rev.* 30:713–17
Lindenberger U, Wenger E, Lövdén M. 2017. Towards a stronger science of human plasticity. *Nat. Rev. Neurosci.* 18:261–62
Lorenz KZ. 1937. The companion in the bird's world. *Auk* 54:245–73
Lövdén M, Bäckman L, Lindenberger U, Schaefer S, Schmiedek F. 2010a. A theoretical framework for the study of adult cognitive plasticity. *Psychol. Bull.* 136:659–76
Lövdén M, Bodammer NC, Kühn S, Kaufmann J, Schütze H, et al. 2010b. Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia* 48:3878–83
Lövdén M, Brehmer Y, Li S-C, Lindenberger U. 2012a. Training-induced compensation versus magnification of individual differences in memory performance. *Front. Hum. Neurosci.* 6:141
Lövdén M, Fratiglioni L, Glymour MM, Lindenberger U, Tucker-Drob EM. 2020. The role of education in lifespan cognitive development. *Psychol. Sci. Public Interest.* In press
Lövdén M, Schaefer S, Noack H, Bodammer NC, Kühn S, et al. 2012b. Spatial navigation training protects the hippocampus against age-related changes during early and late adulthood. *Neurobiol. Aging* 33:620.e9–e22
Lövdén M, Wenger E, Mårtensson J, Lindenberger U, Bäckman L. 2013. Structural brain plasticity in adult learning and development. *Neurosci. Biobehav. Rev.* 37:2296–310
Luders E, Narr KL, Thompson PM, Toga AW. 2009. Neuroanatomical correlates of intelligence. *Intelligence* 37:156–63
Ma L, Wang B, Narayana S, Hazeltine E, Chen X, et al. 2010. Changes in regional activity are accompanied with changes in inter-regional connectivity during 4 weeks motor learning. *Brain Res.* 1318:64–76
Mackey AP, Miller Singley AT, Bunge SA. 2013. Intensive reasoning training alters patterns of brain connectivity at rest. *J. Neurosci.* 33:4796–803
Makino H, Hwang EJ, Hedrick NG, Komiyama T. 2016. Circuit mechanisms of sensorimotor learning. *Neuron* 92:705–21
McGee AW, Yang Y, Fischer QS, Daw NW, Strittmatter SM. 2005. Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor. *Science* 309:2222–26
McNab F, Varrone A, Farde L, Jucaite A, Bystritsky P, et al. 2009. Changes in cortical dopamine D1 receptor binding associated with cognitive training. *Science* 323:800–2
Medaglia JD, Huang W, Karuza EA, Kelkar A, Thompson-Schill SL, et al. 2018. Functional alignment with anatomical networks is associated with cognitive flexibility. *Nat. Hum. Behav.* 2:156–64
Melby-Lervåg M, Hulme C. 2016. There is no convincing evidence that working memory training is effective: a reply to Au et al. 2014 and Karbach and Verhaeghen 2014. *Psychol. Bull. Rev.* 23:324–30
Melby-Lervåg M, Redick TS, Hulme C. 2016. Working memory training does not improve performance on measures of intelligence or other measures of "far transfer": evidence from a meta-analytic review. *Perspect. Psychol. Sci.* 11:512–34
Mery F, Kawecki TJ. 2003. A fitness cost of learning ability in *Drosophila melanogaster*. *Proc. R. Soc. B* 270:2465–69
Meyer D, Bonhoeffer T, Scheuss V. 2014. Balance and stability of synaptic structures during synaptic plasticity. *Neuron* 82:430–43
Molina-Luna K, Hertler B, Buitrago MM, Luft AR. 2008. Motor learning transiently changes cortical somatotopy. *NeuroImage* 40:1748–54

Moore JJ, Ravassard PM, Ho D, Acharya L, Kees AL, et al. 2017. Dynamics of cortical dendritic membrane potential and spikes in freely behaving rats. *Science* 355:eaaj1497

Mosing MA, Madison G, Pedersen NL, Kuja-Halkola R, Ullén F. 2014. Practice does not make perfect: no causal effect of music practice on music ability. *Psychol. Sci.* 25:1795–803

Newcombe NS. 2011. What is neoconstructivism? *Child Dev. Perspect.* 5:157–60

Newell A, Rosenbloom PS. 1981. Mechanisms of skill acquisition and the law of practice. In *Cognitive Skills and Their Acquisition*, ed. JR Anderson, pp. 1–56. Hillsdale, NJ: Erlbaum

Noack H, Lövdén M, Schmiedek F. 2014. On the validity and generality of transfer effects in cognitive training research. *Psychol. Res.* 78:773–89

Nyberg L, Lindenberger U. 2020. Brain maintenance and cognition in old age. In *The Cognitive Neurosciences*, ed. D Poeppel, G Mangun, MS Gazzaniga. Cambridge, MA: MIT Press. 6th ed. In press

Nyberg L, Lövden M, Riklund K, Lindenberger U, Bäckman L. 2012. Memory aging and brain maintenance. *Trends Cogn. Sci.* 16:292–305

Oby ER, Golub MD, Hennig JA, Degenhart AD, Tyler-Kabara EC, et al. 2019. New neural activity patterns emerge with long-term learning. *PNAS* 116:15210–15

Oschwald J, Guye S, Liem F, Rast P, Willis S, et al. 2019. Brain structure and cognitive ability in healthy aging: a review on longitudinal correlated change. *Rev. Neurosci.* In press. **https://doi.org/10.1515/revneuro-2018-0096**

Panchanathan K, Frankenhuis WE. 2016. The evolution of sensitive periods in a model of incremental development. *Proc. R. Soc. B Biol. Sci.* 283:20152439

Patel Y, Shin J, Gowland PA, Pausova Z, Paus T. 2019. Maturation of the human cerebral cortex during adolescence: myelin or dendritic arbor? *Cereb. Cortex* 29:3351–62

Peters AJ, Liu H, Komiyama T. 2017. Learning in the rodent motor cortex. *Annu. Rev. Neurosci.* 40:77–97

Piaget J. 1980. Introduction. In *Les Formes élémentaires de la dialectique*, ed. J Piaget, pp. 9–13. Paris: Gallimard

Plomin R, DeFries JC, Knopik VS, Neiderhiser JM. 2016. Top 10 replicated findings from behavioral genetics. *Perspect. Psychol. Sci.* 11:3–23

Poo MM, Pignatelli M, Ryan TJ, Tonegawa S, Bonhoeffer T, et al. 2016. What is memory? The present state of the engram. *BMC Biol.* 14:40

Pruitt DT, Schmid AN, Danaphongse TT, Flanagan KE, Morrison RA, et al. 2016. Forelimb training drives transient map reorganization in ipsilateral motor cortex. *Behav. Brain Res.* 313:10–16

Putignano E, Lonetti G, Cancedda L, Ratto G, Costa M, et al. 2007. Developmental downregulation of histone posttranslational modifications regulates visual cortical plasticity. *Neuron* 53:747–59

Quallo MM, Price CJ, Ueno K, Asamizuya T, Cheng K, et al. 2009. Gray and white matter changes associated with tool-use learning in macaque monkeys. *PNAS* 106:18379–84

Queenan BN, Ryan TJ, Gazzaniga MS, Gallistel CR. 2017. On the research of time past: the hunt for the substrate of memory. *Ann. N. Y. Acad. Sci.* 1396:108–25

Raz N. 2007. Comment on Greenwood (2007): Which side of plasticity? *Neuropsychology* 21:676–77

Raz N, Daugherty AM. 2018. Pathways to brain aging and their modifiers: Free-Radical-Induced Energetic and Neural Decline in Senescence (FRIENDS) Model—a mini-review. *Gerontology* 64:49–57

Raz N, Schmiedek F, Rodrigue KM, Kennedy KM, Lindenberger U, Lövdén M. 2013. Differential brain shrinkage over 6 months shows limited association with cognitive practice. *Brain Cogn.* 82:171–80

Reed A, Riley J, Carraway R, Carrasco A, Perez C, et al. 2011. Cortical map plasticity improves learning but is not necessary for improved performance. *Neuron* 70:121–31

Rowley CD, Bazin P-L, Tardiff CL, Sehmbi M, Hashim E, et al. 2015. Assessing intracortical myelin in the living human brain using myelinated cortical thickness. *Front. Neurosci.* 9:396

Scarr S, McCartney K. 1983. How people make their own environment: a theory of genotype → environment effects. *Child Dev.* 54:424–35

Schaie KW. 1962. A field-theory approach to age changes in cognitive behavior. *Vita Humana* 5:129–41

Schmiedek F, Lövdén M, Lindenberger U. 2010. Hundred days of cognitive training enhance broad cognitive abilities in adulthood: findings from the COGITO study. *Front. Aging Neurosci.* 2:27

Schmiedek F, Lövdén M, Lindenberger U. 2014. Younger adults show long-term effects of cognitive training on broad cognitive abilities over two years. *Dev. Psychol.* 50:2304–10
Scholz J, Allemang-Grand R, Dazai J, Lerch JP. 2015a. Environmental enrichment is associated with rapid volumetric brain changes in adult mice. *NeuroImage* 109:190–98
Scholz J, Niibori Y, Frankland PW, Lerch JP. 2015b. Rotarod training in mice is associated with changes in brain structure observable with multimodal MRI. *NeuroImage* 107:182–89
Sharpe MJ, Stalnaker T, Schuck NW, Killcross S, Schoenbaum G, Niv Y. 2019. An integrated model of action selection: distinct modes of cortical control of striatal decision making. *Annu. Rev. Psychol.* 70:53–76
Sigal YM, Bae H, Bogart LJ, Hensch TK, Zhuang X. 2019. Structural maturation of cortical perineuronal nets and their perforating synapses revealed by superresolution imaging. *PNAS* 116:7071–76
Simons DJ, Boot WR, Charness N, Gathercole SE, Chabris CF, et al. 2016. Do "brain-training" programs work? *Psychol. Sci. Public Interest* 17:103–86
Skinner BF. 1981. Selection by consequences. *Science* 213:501–4
Smarr BL, Jennings KJ, Driscoll JR, Kriegsfeld LJ. 2014. A time to remember: the role of circadian clocks in learning and memory. *Behav. Neurosci.* 128:283–303
Snyder JS. 2019. Recalibrating the relevance of adult neurogenesis. *Trends Neurosci*. 42:164–78
Stanley JA, Raz N. 2018. Functional magnetic resonance spectroscopy: the "new" MRS for cognitive neuroscience and psychiatry research. *Front. Psychiatry* 9:76
Steele CJ, Zatorre RJ. 2018. Practice makes plasticity. *Nat. Neurosci.* 21:1645–46
Syken J, Grandpre T, Kanold PO, Shatz CJ. 2006. PirB restricts ocular-dominance plasticity in visual cortex. *Science* 313:1795–800
Takahashi H, Funamizu A, Mitsumori Y, Kose H, Kanzaki R. 2010. Progressive plasticity of auditory cortex during appetitive operant conditioning. *Biosystems* 101:37–41
Takesian AE, Hensch TK. 2013. Balancing plasticity/stability across brain development. *Prog. Brain Res.* 207:3–34
Tang E, Giusti C, Baum GL, Gu S, Pollock E, et al. 2017. Developmental increases in white matter network controllability support a growing diversity of brain dynamics. *Nat. Commun.* 8:1252
Tau GZ, Peterson BS. 2010. Normal development of brain circuits. *Neuropsychopharmacology* 35:147–68
Taubert M, Mehnert J, Pleger B, Villringer A. 2016. Rapid and specific gray matter changes in M1 induced by balance training. *NeuroImage* 133:399–407
Thorndike EL. 1898. *Animal Intelligence: An Experimental Study of the Associative Processes in Animals*. New York: Macmillan
Tonegawa S, Pignatelli M, Roy DS, Ryan TJ. 2015. Memory engram storage and retrieval. *Curr. Opin. Neurobiol.* 35:101–9
Tucker-Drob EM. 2017. How do individual experiences aggregate to shape personality development? *Eur. J. Personal.* 31:529–95
Uhlhaas PJ, Roux F, Rodriguez E, Rotarska-Jagiela A, Singer W. 2009. Neural synchrony and the development of cortical networks. *Trends Cogn. Sci.* 14:72–80
Ullén F, Hambrick DZ, Mosing MA. 2016. Rethinking expertise: a multifactorial gene–environment interaction model of expert performance. *Psychol. Bull.* 142:427–46
Vendetti MS, Bunge S. 2014. Evolutionary and developmental changes in the lateral frontoparetial network: A little goes a long way for higher-level cognition. *Neuron* 84:906–17
von Bastian CC, Oberauer K. 2014. Effects and mechanisms of working memory training: a review. *Psychol. Res.* 78:803–20
Voss MW, Vivar C, Kramer AF, van Praag H. 2013. Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn. Sci.* 17:525–44
Waehnert MD, Dinse J, Weiss M, Streicher MN, Waehnert P, et al. 2014. Anatomically motivated modeling of cortical laminae. *NeuroImage* 93:210–20
Walhovd KB, Lövdén M. 2020. A lifespan perspective on human neurocognitive plasticity. In *The Cognitive Neurosciences*, ed. D Poeppel, G Mangun, MS Gazzaniga. Cambridge, MA: MIT Press. 6th ed. In press

Wenger E, Brozzoli C, Lindenberger U, Lövdén M. 2017a. Expansion and renormalization of human brain structure during skill acquisition. *Trends Cogn. Sci.* 21:930–39

Wenger E, Kuhn S, Verrel J, Martensson J, Bodammer NC, et al. 2017b. Repeated structural imaging reveals nonlinear progression of experience-dependent volume changes in human motor cortex. *Cereb. Cortex* 27:2911–25

Werker JF, Hensch TK. 2015. Critical periods in speech perception: new directions. *Annu. Rev. Psychol.* 66:173–96

Wiesel TN, Hubel DH. 1963. Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J. Neurophysiol.* 26:1003–17

Wiesel TN, Hubel DH. 1965. Extent of recovery from the effects of visual deprivation in kittens. *J. Neurophysiol.* 28:1060–72

Wiestler T, Diedrichsen J. 2013. Skill learning strengthens cortical representations of motor sequences. *eLife* 2:e00801

Wymbs NF, Grafton ST. 2015. The human motor system supports sequence-specific representations over multiple training-dependent timescales. *Cereb. Cortex* 25:4213–25

Xu T, Yu X, Perlik AJ, Tobin WF, Zweig JA, et al. 2009. Rapid formation and selective stabilization of synapses for enduring motor memories. *Nature* 462:915–19

Yang G, Pan F, Gan WB. 2009. Stably maintained dendritic spines are associated with lifelong memories. *Nature* 462:920–24

Yotsumoto Y, Watanabe T, Sasaki Y. 2008. Different dynamics of performance and brain activation in the time course of perceptual learning. *Neuron* 57:827–33

Yuan P, Raz N. 2014. Prefrontal cortex and executive functions in healthy adults: a meta-analysis of structural neuroimaging studies. *Neurosci. Biobehav. Rev.* 42:180–92

Zatorre RJ. 2013. Predispositions and plasticity in music and speech learning: neural correlates and implications. *Science* 342:585–89

Zatorre RJ, Fields RD, Johansen-Berg H. 2012. Plasticity in gray and white: neuroimaging changes in brain structure during learning. *Nat. Neurosci.* 15:528–36

Ziegler G, Hauser TU, Moutoussis M, Bullmore ET, Goodyer IM, et al. 2019. Compulsivity and impulsivity traits linked to attenuated developmental frontostriatal myelination trajectories. *Nat. Neurosci.* 22:992–99

Zinke K, Zeintl M, Rose NS, Putzmann J, Pydde A, Kliegel M. 2014. Working memory training and transfer in older adults: effects of age, baseline performance, and training gains. *Dev. Psychol.* 50:304–15