

Perspective

From animal models to human individuality: Integrative approaches to the study of brain plasticity

Maïke Hille,^{1,2,*} Simone Kühn,^{2,3,4} Gerd Kempermann,^{5,6} Tobias Bonhoeffer,⁷ and Ulfman Lindenberger^{1,4,*}

¹Center for Lifespan Psychology, Max Planck Institute for Human Development, Berlin, Germany

²Center for Environmental Neuroscience, Max Planck Institute for Human Development, Berlin, Germany

³Clinic and Policlinic for Psychiatry and Psychotherapy, University Clinic Hamburg-Eppendorf, Hamburg, Germany

⁴Max Planck UCL Centre for Computational Psychiatry and Ageing Research, Berlin, Germany, and London, UK

⁵German Center for Neurodegenerative Diseases (DZNE), Dresden, Germany

⁶CRTD – Center for Regenerative Therapies Dresden, TU Dresden, Dresden, Germany

⁷Synapses-Circuits-Plasticity, Max Planck Institute for Biological Intelligence, Martinsried, Germany

*Correspondence: hille@mpib-berlin.mpg.de (M.H.), seklindenberger@mpib-berlin.mpg.de (U.L.)

<https://doi.org/10.1016/j.neuron.2024.10.006>

SUMMARY

Plasticity allows organisms to form lasting adaptive changes in neural structures in response to interactions with the environment. It serves both species-general functions and individualized skill acquisition. To better understand human plasticity, we need to strengthen the dialogue between human research and animal models. Therefore, we propose to (1) enhance the interpretability of macroscopic methods used in human research by complementing molecular and fine-structural measures used in animals with such macroscopic methods, preferably applied to the same animals, to create macroscopic metrics common to both examined species; (2) launch dedicated cross-species research programs, using either well-controlled experimental paradigms, such as motor skill acquisition, or more naturalistic environments, where individuals of either species are observed in their habitats; and (3) develop conceptual and computational models linking molecular and fine-structural events to phenomena accessible by macroscopic methods. In concert, these three component strategies can foster new insights into the nature of plastic change.

FROM ANIMAL MODELS TO HUMAN INDIVIDUALITY: INTEGRATIVE APPROACHES TO THE STUDY OF BRAIN PLASTICITY

Neuronal plasticity is not universally defined and used differently in different disciplines and contexts. Here, we define plasticity as the capacity of organisms to form lasting but reversible structural and related functional changes of neural connections in response to interactions with the environment. According to an influential distinction introduced by Greenough and colleagues,¹ plasticity comes in two ontogenetically distinct forms. One is experience expectant and enables organisms to meet species-specific affordances that allow for behavioral development, such as imprinting² or basic sensory functions.³ The close link between maturation and plasticity is evident in this form of plasticity. The other form is experience dependent and enables individuals to respond and adapt to the specific and often individualized challenges of the environment throughout ontogeny, such as during the acquisition of a specialized skill.

As noted elsewhere,⁴ the distinction between experience expectancy and experience dependency reflects gradual differences in the scope and developmental timing of plastic episodes rather than two perfectly separable classes of phenomena.

Mechanisms of learning play a critical role in both experience-expectant and experience-dependent plasticity. Furthermore, the experience-dependent ability to acquire skills that are idiosyncratic to the environmental niche of a given individual is itself an adaptation that has resulted from natural selection and hence can be considered as a broader form of experience expectancy. Therefore, the mechanisms implementing either type of plasticity might be similar.^{4–6} However, the more fundamental and procedural or sensorimotor the acquired skill or learned behavior is, the more robust and invariant to further change it appears to be. The acquisition of binocular vision, for example, is clearly a process involving plastic changes in neuronal networks, but these tend to become very stable and are not easily unlearned. Plasticity in the context of declarative memory of facts and episodes might share mechanisms with procedural learning (and imprinting) but remains much more malleable.

For research on any form of plasticity, however, we observe a substantial gap between animal models and research with humans.⁷ This gap exists for good reason. Many of the sophisticated experimental methods at the level of molecules, cells, and cellular microenvironments that are commonplace in animal studies are not applicable in research with humans. As a consequence, our mechanistic understanding of human brain plasticity



typically has to be inferred from animal models and is based on assumptions that often cannot be validated directly. This is paradoxical insofar as much of the work on plastic change in animals is undertaken with the goal to better understand the mechanisms underlying presumably equivalent forms of brain plasticity in humans, be it in the context of normal and abnormal development, of skill acquisition, or of learning and memory.

There is a clear need to promote research designs and concepts that aim at bridging the experimental and conceptual gaps that exist between animal models and research with humans. Integrating the mechanistic understanding from animal models at the level of gene-environment interactions, molecular processes, and fine-structural modifications with the wealth of sophisticated neuroimaging and psychological studies in humans would pave the way for more comprehensive mechanistic models of plasticity in health and disease, which may eventually make it possible to target plasticity in humans more effectively for preventive or therapeutic reasons. In a similar vein, the desire to understand how behavior-dependent plasticity drives and shapes individual differences in human connectomes can also inform the design of novel animal paradigms.^{8–12}

To promote a more comprehensive mechanistic understanding of plasticity in humans and to strengthen an overarching life-span perspective on the emergence of individuality, we need to identify existing points of contact between animal models and human research and create new ones.^{13,14} In this perspective article, we present some thoughts on how progress toward this goal can be made. In doing so, we focus on three interrelated components.

First, we argue that the interpretability of macroscopic methods in research with humans can be greatly enhanced by complementing the wealth of molecular and fine-structural measures used in animals with macroscopic methods, preferably applied to the same individuals,¹⁵ with the goal to create macroscopic metrics common to both species examined. Regarding macroscopic methods, we primarily refer to structural magnetic resonance imaging (sMRI), which includes quantitative parametric mapping^{16,17} and *in vivo* histology at high field strengths. In addition, we occasionally also refer to diffusion tensor imaging (DTI), positron emission tomography (PET) imaging, magnetic resonance spectroscopy (MRS), and electroencephalography (EEG); see also Box 1.

Second, we need to develop coordinated research programs that capture mechanistic complexity across scales (e.g., from genes to behavior) and across functional domains (e.g., sensory, motor, cognitive, emotional, and social), again in both animals and humans. The development of these programs is not a one-way street but requires information flow in both directions. On the one hand, central questions of human plasticity, such as the emergence of individuality, need to guide the design of animal models.⁸ On the other hand, the elaborate research on environmental enrichment using animal models can guide the search for relevant environmental features in human habitats.

Third, we need conceptual and computational models that link molecular and fine-structural events, such as the plasticity of synapses, dendrites, and spines,^{44,45} to phenomena that are accessible by macroscopic methods. We highlight the need to develop models and theories that bridge scales and domains

of measurement by specifying how mechanisms identified in animal models map onto macroscopic structural and correlated functional changes that can be measured in humans and present one specific theory of this kind.^{4,6}

In the remainder of this article, we further delineate each of these three components and provide examples of existing or future research projects to illustrate their potential. In doing so, we focus on structural aspects of brain plasticity in humans. Functional connectivity changes are considered only if they are likely to represent the functional consequences of a hypothesized structural change.⁴⁶

COMPONENT 1: STRENGTHENING THE METHODS INTERFACE

In rodents and other animals, neural plasticity can be imaged at the level of single cells *in vivo* using two-photon microscopy.^{45,47} Cells can be analyzed and clustered by methods such as single-cell sequencing to provide insight into subtle changes in tissue composition and cellular function. In humans, sMRI provides measurements at much lower resolution and specificity and without access to the molecular level. Despite important advances in neuroscientific techniques in humans, such as sMRI, fMRI, and MRS at high field strengths as well as PET aided by artificial intelligence (AI) (see Box 1), noninvasive structural imaging at the single-cell level is currently impossible and does not seem within close reach. In light of these massive differences in measurement, it is helpful to create overlapping datasets between animal models and human research in domains accessible in both examined species while making use of advanced cellular and molecular methods in animals and of psychological studies and biophysical modeling in humans (see Figure 1).⁷

Integrating data across species, scales, domains, and time

Morphometric measures derived from sMRI can be acquired in both humans and other animals, often by utilizing close to identical data-analysis processing pipelines. On the animal side, coarse volumetric measures can then be related to cellular measures acquired with invasive methods, like live cellular imaging and post-mortem quantitative histology, electron-microscopic tissue reconstructions, transcriptomic profiling, and more. The integration of data across scales and domains in the same animals can provide insights about how volume changes map onto underlying cellular changes, which may then be extrapolated to humans, for whom cellular and molecular measurements are not available.

Clearly, one-to-one correspondences between cellular changes and changes in sMRI image features are highly unlikely. Instead, changes in sMRI images will typically represent the net result of multiple physiological mechanisms. Still, obtaining measurements of plasticity-related changes at both microscopic and macroscopic levels within the same animal can enhance the physiological interpretability of sMRI image changes in animals, and consequently also in humans, by reducing the number of candidate mechanisms that these changes express.

Gray-matter changes have been found in all kinds of physiological and pathological situations in humans and animals. To

Box 1. Advances in imaging methods

Studies with rodents suggest that multiple cellular mechanisms contribute to plasticity-related gray-matter volume changes. The underlying mechanisms that contribute to such changes are likely to differ across brain regions, task domains, and stages of plastic change. To enhance the physiological interpretability of measures amenable to human research, it is imperative to assess the full scope of biological mechanisms at the cellular and molecular level in addition to structural changes at the macroscopic level in animals to obtain a comprehensive picture of their associations.

Quantitative MRI (qMRI). In combination with biophysical modeling, advanced neuroimaging methods can improve the interpretability of morphometric results by approximating microstructural tissue properties of the brain from MRI parameters in both humans and other animals.^{16,17} qMRI assesses physical quantities such as relaxation time or magnetization transfer in a voxel-wise manner. By applying biophysical modeling to a variety of qMRI parameters using multi-parameter mapping,¹⁸ the resulting data can be converted into physiologically interpretable metrics, such as iron content or axonal diameters. For example, Azzarito et al.¹⁹ used qMRI to investigate microstructural changes in the gray and white matter of healthy young adults undergoing 4 weeks of complex motor task training. Among other parameters, they assessed the longitudinal relaxation rate ($R1 = 1/T1$) and magnetization transfer saturation (MT_{sat}). Given that higher myelin content shortens the T1 relaxation time, R1 served as a marker for myelin concentration, whereas MT_{sat} is assumed to indicate myelin density by measuring magnetization exchange between myelin macromolecules and water. During training, markers followed a non-monotonic temporal pattern in the left posterior cerebellum, initially decreasing and then renormalizing by the end of the learning period. According to the authors, the observed changes may be related to myelin remodeling, alterations in local tissue composition, or both. Analogous qMRI measurements in animal models combined with microscopic methods are likely to reduce these interpretational ambiguities.¹⁹

In vivo MRI histology. High-field strength MRI approaches (e.g., 7 Tesla and higher), which seek to resolve the laminar structure of the cortical sheath,²⁰ are equally promising. Such methods may permit the observation of layer-specific plastic changes in response to learning.²¹ Currently the focus of available biophysical models is on white-matter microstructural features, such as MR g-ratio associated with axonal conduction velocity.²² Advances in biophysical modeling are needed to derive estimates of gray-matter properties²³ such as neuronal density,²⁴ dendritic density,²⁵ and soma density.^{26,27}

Positron emission tomography (PET). The design of new radioligands and advances in image reconstruction based on AI open up new opportunities for the use of PET in research on plasticity.²⁸ For instance, with the help of radioligands binding to the synaptic vesicle protein 2A (SV2A), PET can yield *in vivo* estimates of synaptic density in humans,^{29–31} including changes in synaptic density in the course of skill acquisition. Specifically, setting up an intervention study in which participants acquire a new skill and are assessed with PET together with MRI across several occasions would make it possible to examine whether regional synaptic density changes correlate with gray-matter volume changes (M. Lövdén, personal communication). PET allows for *in vivo* molecular and metabolic imaging but requires radioactive isotopes. Therefore, PET measurements have typically been restricted to the assessment of a single radioligand in humans. Recent methodological work suggests that radiation dosage can be drastically reduced using AI-assisted image reconstruction.³² This may enable several PET markers to be administered to the same individual in close succession, resulting in a multidimensional and dynamic picture of plasticity-related metabolic and neurochemical changes in the human brain.

Magnetic resonance spectroscopy (MRS). Using MRS changes in excitatory-inhibitory (E/I) balance can be assessed non-invasively as the ratio of glutamate (Glu) to γ -aminobutyric acid (GABA). E/I balance is thought to regulate the induction and expression of long-term potentiation (LTP) and long-term depression (LTD), two forms of synaptic plasticity that enhance or weaken synaptic transmission. Hence, E/I balance plays an important role in modulating synaptic plasticity.³³ More widely available 7-Tesla MRI systems greatly facilitate the simultaneous quantification of GABA and Glu.³⁴

Imaging of genetically modified animal models. In addition to correlating cellular changes with gray-matter volume changes, a complementary strategy consists in identifying relevant mechanisms using genetically modified animal models in combination with multi-modal neuroimaging techniques. For instance, one possible approach to find out whether increased synapse formation is an underlying biological mechanism of motor cortex gray-matter volume increases in response to motor learning is to block the formation of new synapses in a knockout mouse model by inactivating genes known to be involved in synapse formation.³⁵ Synapse formation can be measured via two-photon microscopy during training of a task, while sMRI would be used to find out whether a reduction in learning-induced synapse formation reduces or eliminates learning-induced volume increases in task-specific brain regions. In addition to investigating dendritic spine formation, knockout mice models can be used to examine spine stability³⁶ or the clustering of dendritic spines³⁷ during learning.

Human genome-wide association studies (GWASs). In combination with transcriptomic profiles, genome-wide association studies (GWASs) can help to identify which cell types are associated with macroscopic structural brain changes^{38,39} and cognitive phenotypes. For example, Lam and colleagues⁴⁰ studied the genetic basis of individual differences in cognitive performance and found that neurons and their synaptic mechanisms, rather than oligodendrocytes and astrocytes, were the main carriers of gene-related variation in cognition. Individual differences in cognitive performance tend to be correlated with macroscopic aspects of brain structure, such as regional gray-matter volume or thickness.⁴¹ Exact definitions of brain regions and cell types are notoriously difficult. To bridge the gap between genes and brain structure, transcriptomic profiles can help to reveal in which brain

(Continued on next page)

Box 1. Continued

regions and cell-type genes are potentially expressed.³⁸ New insights into single-cell transcriptomics have profoundly influenced and advanced the definition of cell types and their functional states.^{42,43} At the molecular level, plasticity is characterized by epigenetic changes that represent such altered states and are considered the molecular equivalents of plasticity and its consequences at the level of cells.

date, only a few studies have combined sMRI measures with microscopic measures in animals to relate changes in gray-matter volume to putative underlying cellular mechanisms, usually through post-mortem immunohistochemistry and biochemical or molecular measures. Findings from rodent studies on structural changes supposedly indicative of plasticity are mixed, suggesting several possible cellular mechanisms that might contribute to gray-matter volume changes observable at the macroscopic level. Using voxel-based morphometry (VBM) as well as histology and MRS in mouse brains, gray-matter volume changes in the hippocampus have been associated with adult hippocampal neurogenesis and changes in glutamate (Glu) levels in response to wheel running.^{48–50} Also, decrements in gray-matter concentrations in the CA1 region of the hippocampus as assessed by sMRI have been found to correlate with reductions in the number of neurons in rats after cardiac arrest and subsequent cardiopulmonary resuscitation.⁵¹ Lerch et al.⁵² have suggested that the remodeling of neuronal processes, rather than neurogenesis or neuron number, accounts for hippocampal gray-matter volume increases during spatial learning in mice. In sum, gray-matter changes have been found in all kinds of experimental situations in both humans⁵³ and rodents, involving either losses⁵¹ or gains⁵² in structure, function, and behavior. What needs to be further strengthened is the link of these findings to what is happening functionally and structurally at finer-grained levels of analysis.

In regions other than the hippocampus, sMRI-based changes in gray-matter volume have been linked to changes in (1) dendritic volume in the anterior cingulate cortex following stress⁵⁴; (2) dendritic spine density, spine head diameter, and spine length in the auditory cortex after auditory fear conditioning⁵⁵; (3) dendrite length, number of spines, and structural changes in astrocytes in visual and lateral entorhinal cortex in response to monocular deprivation⁵⁶; and (4) the number and size of microglia in the striatum in a rat model of levodopa-induced dyskinesia.⁵⁷

Mediavilla and colleagues¹⁵ investigated mice during learning of a forelimb reaching task with longitudinal *in vivo* sMRI in addition to *ex vivo* cross-sectional myelin immunoreactivity. They found that nonlinear decreases in gray-matter volume juxtaposed with nonlinear increases in white-matter volume within gray matter were associated with non-linear changes in myelin immunoreactivity that seemed to be influenced by length density of myelinated axons, calculated as the length of myelinated fibers per tissue volume unit. The authors concluded that myelin might be a major component of structural changes observed at the macroscopic level by VBM during motor learning.¹⁵ With *ex vivo* methods such as the immunoreactivity data collected by Mediavilla and colleagues, physiological changes within the same individuals cannot be

observed longitudinally. This problem can be circumvented by using repetitive two-photon *in vivo* microscopy imaging in combination with sMRI. In principle, the joint use of the two methods can help to identify the underlying cellular basis of volume changes in longitudinal study designs, but many details remain challenging, in great part due to the limited size of the field of view (FOV) when using *in vivo* microscopy. Still, using this strategy, Asan and colleagues⁵⁸ suggested that local cell density, spatial arrangement of cells as well as cell-type composition all contribute to observable macroscopic volume changes. Although their approach is not free of assumptions about the reference volume (i.e., the volume of the entire structure of interest) and its change over time, the study is nevertheless a strong example of how the parallel use of a given method (i.e., sMRI) that can be applied to both humans and rodents in combination with one that is only applicable in animals (i.e., *in vivo* two-photon microscopy) can be used to gain insights into the dynamics of plasticity across scales.

Beyond work with rodents, animal studies addressing the relationship between macroscopic and microscopic brain measures in the course of plastic change are sparse. In monkeys it is possible to administer very similar cognitive tests as in humans; in addition, the brains of humans are anatomically more similar to monkeys' than to rodents'. Several studies have shown that combining *in vivo* MRI and microscopy is technically possible in macaques^{59,60} and in marmosets.^{61–63} However, so far, no study has used a multimodal approach to investigate structural plasticity at different spatial scales in these or other primate species.

Challenges in linking animal models to human research

Attempts to bridge the gap between research on plasticity in animals and humans face various difficulties. One pivotal problem is to define a common brain space mapping homologous brain areas between different species and to develop applicable ontologies across the many aspects of the relevant research. Automated procedures are available, such as those using a parcellation-based approach based on anatomical features.⁶⁴ Alternatively, one may resort to higher levels of abstraction, such as brain regions defined on the basis of equivalent functional brain activity profiles.⁶⁵ Generally, the organization of the mammalian brain is sufficiently well conserved to make use of the general cellular architecture for matching homologous cell types. Note, however, that Hodge et al.⁶⁶ have observed species- and region-specific differences in cell types that are likely to affect microcircuit function. Therefore, the extent to which the features under study are similar across species needs to be examined carefully in each individual case.⁶⁶

In addition to delineating homologous anatomical and molecular features across species, it is equally important to align data from humans and other species along an ontogenetic axis

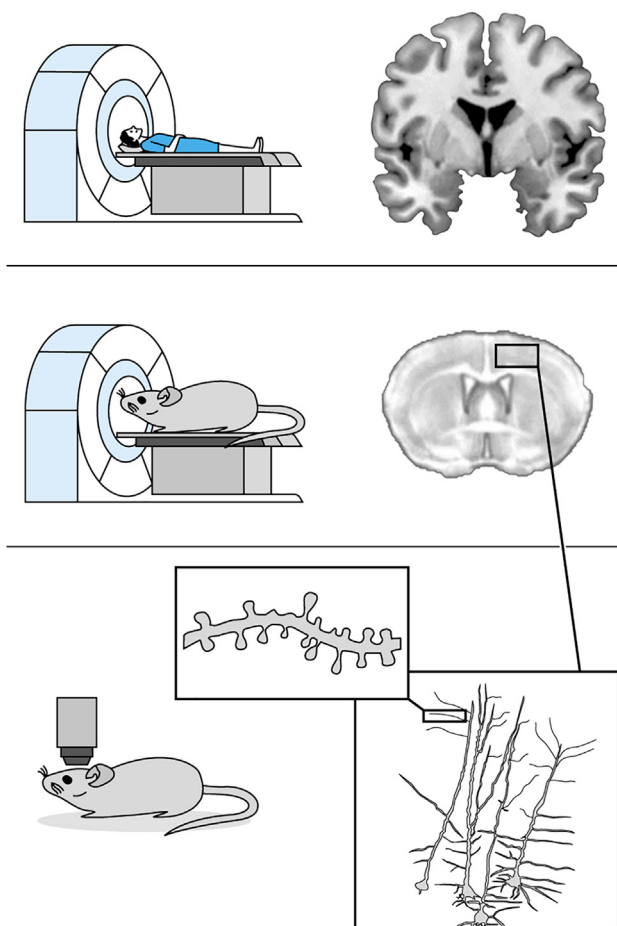


Figure 1. Strengthening the methods interface

In both humans and animals, estimates of longitudinal morphometric changes can be derived from sMRI. On the animal side, additional cellular measures can be acquired, in particular using *in vivo* imaging techniques. Applying microscopic and macroscopic methods in the same animals can reveal the extent to which coarse volume changes can be mapped onto fine-grained cellular changes. The results may then be extrapolated to humans, where no direct microscopic measures are available.⁷

defined by the pacing of maturational and senescent brain changes.^{67–69} In most studies with mice, animals older than 60 days are referred to as “adults.” In the literature, researchers most often investigate mice between 6 and 20 weeks. Responses to a questionnaire suggest that researchers often choose this age period for practical reasons.⁷⁰ While brain volume seems to stabilize in mice at 3 weeks, cortical thickness and myelination are still undergoing age-related maturational changes until 3 months of age,⁷¹ and concomitant microstructural changes take place until at least 4 months of age.⁷²

Furthermore, ontogenetic changes in the degree, operation, and path dependency of plastic mechanisms need to be taken into account. For instance, experience-dependent plasticity during skill acquisition in adulthood may build on experience-expectant plasticity during critical periods. In more general terms, the results of earlier periods of plasticity are likely to influence the onset and outcome of later plastic episodes.^{73–75} At the level of neurotrans-

mitters and throughout ontogeny, cortical plasticity is regulated by changes in the balance between excitation and inhibition.⁷⁶ The regulation of inhibition itself depends upon maturation and changes during the transition from early life to adulthood.^{76,77}

Another prerequisite for comparing plastic brain changes across species is to assemble and coordinate analysis pipelines that are suitable for brains that differ greatly in size and complexity. Usually, in humans, the analysis of volume changes requires segmenting the brain into different tissue classes using established toolboxes.^{78,79} Segmentation of imaged animal brains is sometimes more difficult, reflecting differences in image contrasts and less clearly defined brain structures. Furthermore, analysis procedures are usually less standardized in animal models than in humans. To establish common ground across species and warrant between-species comparisons, progress needs to be made in establishing processing pipelines applicable to both human and non-human brains. One option in need of further validation is the use of deformation-based morphometry in combination with multi-atlas segmentation approaches.^{64,80} This approach bears the potential to map neuroanatomical regions based on cytoarchitectonic and MRI-derived human atlases onto cytoarchitectonic mouse atlases to identify brain regions that are homologous across the two species.

A potential difference between animal and human studies is the degree of stress that the study procedure elicits. In longitudinal animal studies, multiple *in vivo* imaging sessions might lead to stress during handling and experimental preparation.⁸¹ In particular, oxidative stress due to multiple anesthesia exposures might compromise the validity of both neural and behavioral data.^{82,83} It is therefore recommended to run parallel sets of animals as control groups to gauge the effects of repeated anesthesia exposure.

Another between-species difference in methodology concerns spatial scope and resolution. Microscopic imaging methods are spatially limited. While anatomical MR images are usually analyzed on a whole-brain level, *in vivo* imaging methods at the subcellular level are constrained to a very small FOV. For example, two-photon microscopy in mice typically allows for a FOV with a surface size below 1 mm².⁸⁴ When combining measures at different spatial scales, it is important to find a suitable registration method to ensure correct mapping between the different imaging modalities. One example is to use blood vessel branching points as landmarks in two-photon microscopy stacks and sMRI volumes, given that they are visible in both imaging modalities.⁵⁸ Advances in neuroimaging methods that allow for a larger FOV while maintaining synaptic resolution will help to identify corresponding mechanisms of plasticity at different spatial levels.^{85–87}

Limits to causality attribution

Even if measures from microscopic and macroscopic levels of analysis have been obtained repeatedly from the same animals in the course of skill acquisition and methodological precautions have been taken, it still remains challenging to draw causal inferences that link behaviorally relevant mechanisms to changes discernible by macroscopic methods. Let us assume that there are sets of (1) microscopic variables, $X_{1...n}$, (2) macroscopic variables, $Y_{1...n}$, and (3) behavioral variables,

$Z_{1...n}$, and that all three sets have been observed repeatedly over time. The time-ordered nature of these sets allows researchers to analyze lead-lag relations among them.^{88–91} Based on such analyses, it may turn out that changes in a subset of set X variables precede and predict changes in a (presumably smaller) subset of Y variables, which in turn are linked to changes in a subset of Z variables. Such results are informative, as they point researchers to those subsets in X, Y, and Z that show correlated patterns of change. However, delineating such lead-lag relations does not imply causality. For instance, changes in Y may be influenced by several changes in X, some of which are causal for changes in Z, while others are not. To move closer toward inferring causality, we need to introduce experimental manipulations that affect mechanisms captured by the X set of variables and observe downstream effects on sets Y and Z. In addition, we need to make sure that interpretations of data at the macroscopic level are consistent with what is known about the underlying physiology assessed at the microscopic level.⁹²

COMPONENT 2: DESIGNING ANALOGOUS EXPERIMENTAL PARADIGMS AND ENVIRONMENTS FOR ANIMALS AND HUMANS

Linking research with animal models to human research requires an explicit effort to develop analogous experimental paradigms and comparable behavioral tasks that can be used to elicit structural brain plasticity on either side (see Box 2). This implies two important but not fully compatible requirements. On the one hand, one would like the target behavior to be sufficiently similar across species to enable valid comparisons; on the other, the task that is used to elicit these behaviors should be ethologically and ecologically meaningful in both species. Given that species have adapted to different environments, neither of these two requirements can be met in full. In our view, there are at least two productive ways of dealing with this problem. First, we can devise human analogs of well-researched animal models to implement the kind of microscopic-macroscopic method overlap described in the previous section. This strategy probably works best when studying the experience-dependent acquisition of specific skills that are arguably relatively similar and meaningful in both examined species. Examples are grasping food items, encoding episodic memories, navigating new spaces, and various forms of perceptual learning.

Second, we can move to a different level of abstraction and devise animal models that help to uncover mechanisms of brain plasticity that act as motors of individuality across different species, often reflecting a natural mix of experience-expectant and experience-dependent plasticity. This strategy entails members of the model species being followed longitudinally in their natural habitats to observe the way in which plasticity contributes to their individual development.

Whereas the first strategy aims to bring human research closer to animal models, the second tries to bring animal models closer to the richness of human experience. Importantly, the latter strategy can also feedback onto human research, as it forces researchers to think about the dimensions that shape and enrich human ecologies. Each of these two strategies comes with

different strengths and weaknesses; whereas the former reduces the richness of behaviors to definable tasks, the latter attempts to deconstruct the complexity of behavior post hoc. In the following, we illustrate both strategies with research from our own ongoing work.

Finding common ground across species: Studying skill acquisition in mice and humans

The acquisition of new skills is likely to induce brain plasticity in primary brain areas such as the motor, auditory, or visual cortices, depending on the nature of the skill in question. For example, both rodents and humans are capable of acquiring motor skills in the form of complex grasping movements. Skilled reaching is comparable across humans and rodents, as the succession of hand-shaping movements is homologous in the sense that they follow similar temporal and spatial patterns.⁹³

We are currently conducting a collaborative study in which both mice and humans learn a fine motor skill. Over several days mice are trained in the single-pellet reaching task,⁹⁴ in which they learn to grasp a small food item through a narrow slit in an acrylic glass wall, using their preferred paw. In the corresponding human task, the participants undergo a daily training regime with an adapted reaching task using chopsticks (see Figure 2). Thus, both mice and humans learn to reach through a narrow slit and grasp a little food object that is then transported over a short distance. Our expectation is that the use of such corresponding motor tasks will result in analogous learning curves and will induce similar mechanisms promoting plasticity in the motor cortices of either species.

A limitation of the motor task is that humans are required to use a tool instead of learning to grasp solely with their hands, given their pre-existing natural proficiency in single-hand grasping. However, finding a task for humans that simulates the animal movement of acquiring a new kind of grasping without the addition of a tool proved to be challenging. In this context, it is worth noting that there is evidence in humans suggesting that the neural responses for graspable food items show some similarities to the responses for tool stimuli.⁹⁵ Another distinction between the animal and human tasks is that the mice are food-restricted and, after successfully grasping the food pellet, consume it immediately as a reward. By contrast, humans place the food item into a bowl and receive a secondary reward (i.e., a monetary reimbursement for participation) but are allowed to eat the transported sweets after successful completion of the whole task.

Both humans and mice undergo multiple sMRI measurements to acquire macroscopic anatomical measures (e.g., gray-matter volume estimates) at different time points during the time course of training. In mice, different cellular measures such as the number and morphology of dendritic spines, number and morphology of astrocytes, length of myelin sheaths, and diameter and density of blood vessels are recorded and quantified. In addition, the motor cortices of the mice are examined histologically post-mortem. Assessing plasticity-related changes at macroscopic and microscopic levels in the same animals will allow us to directly relate these measures and their variation over time to each other. Using this approach, we can study brain changes over time to determine

Box 2. Challenges in developing analogous paradigms across humans and animals

Attempts to overcome the gap between animal and human research on plasticity by developing analogous paradigms for animals and humans face several challenges that can curtail their validity. These challenges differ between skill-acquisition studies in rather well-controlled experimental settings, on the one hand, and enrichment paradigms, on the other.

In relation to skill-acquisition studies, we note the following concerns with respect to their validity:

- (1) *Comparable pair of tasks.* A major challenge in skill-acquisition studies with animals and humans is to decide on the appropriate analogy between the tasks. While human participants can be instructed in tasks and provided with oral feedback, there is no direct way to communicate task rules to animals. Instead, they generally learn the task on the basis of trial and error, and this may lead to between-species differences in task representations and learning mechanisms.¹⁶⁹ Additionally, adjusting task difficulty becomes imperative to achieve comparable behavioral outputs, given potential behavioral proficiency variations between species. In addition to the grasping paradigm summarized above, promising examples of other behavioral tasks studied conjointly in animals and humans include spatial navigation,¹⁷⁰ inferential reasoning,¹⁷¹ inhibition control,¹⁷² as well as memory formation in infant mice and humans.^{69,165,166}
- (2) *Comparable spacing of observations.* The main goal of skill-acquisition studies is to observe manifestations of plasticity in brain and behavior over time. Humans and animals are likely to differ in initial proficiency and learning rate, which raises the question of how to align learning trajectories across species. Which equivalence relation governs the number of trials in humans and the animal species under investigation? At what points in time should brain measures be taken to provide assessments that reflect equivalent levels of skill? Plastic responses to challenges occur on multiple timescales, and some of them are likely to be non-linear. Capturing changes too early, too late, and without a sufficiently large number of occasions can result in incomplete or even distorted pictures of underlying processes. These concerns are all amplified when trying to align measurement protocols across species.
- (3) *Training to criterion.* Relatedly, it is critical that all members of both species are trained to approximately the same criterion level, be it to study plastic changes in the course of skill acquisition or to study subsequent retention and forgetting once the skill has been acquired. The methodological lessons learned from conducting age-comparative research on skill acquisition and forgetting in humans are instructive in this regard.^{173–175} Specifically, training a novel skill to asymptotic levels of performance helps to reduce pre-experimental influences and increase the interpretability of neural and behavioral findings.¹⁷⁶
- (4) *Comparable ontogenetic status.* To better understand similarities and differences of the mechanisms that regulate brain plasticity during different periods of development and to study the effects of earlier on later plasticity, we need to relate developmental animal models to developmental human data.⁶⁹ This requires the use of longitudinal designs that are matched on developmental age across species. Aligning two different species, such as mice and humans, on developmental age is inherently problematic. One recently proposed approach is to take epigenetic clocks generated by DNA methylation patterns as a comparable yardstick across mammalian species.¹⁷⁷ DNA methylation parameters can be adjusted for between-species differences in lifespan and may ease across-species alignment.^{177,178}
- (5) *Primary versus secondary rewards.* Learning tasks in laboratory experiments typically entail rewards to motivate participation. Whereas animals receive primary rewards, such as food or sweetened water, humans typically receive secondary awards (e.g., money). In most studies with animals, food restriction in combination with a food reward is used to incentivize performance. Across-species differences in reward schedules need to be critically evaluated to ensure that learning mechanisms and their neural substrate are not differentially influenced by reward type.¹⁷⁹ This may entail an increased reliance on primary rewards in experiments with human participants.

Enrichment paradigms for animals range from more well-controlled cage settings to quasi-natural living environments. These paradigms have in common that they create observational conditions that allow researchers to link individual differences in brain plasticity to individual differences in behavioral development. At the same time, the reduction in experimental control relative to skill-acquisition studies comes with ambiguities and confounds that need to be kept in mind. The following challenges seem particularly relevant:

- (1) *Physical versus social aspects of environmental enrichment.* In environmental enrichment settings, such as the individuality paradigm, it is notoriously difficult to delineate and isolate the various aspects or “active ingredients” of the environment that trigger plasticity. The classical literature on the subject distinguishes sensory, motor, cognitive, and social influences but has not attempted a unifying theory.¹⁴ Physical aspects of the environment, such as more complex stimuli to process, more things to play with, and more opportunities to exercise, and social aspects of the environment, such as living in a large group with more frequent and complex social interactions among conspecifics, are often inherently confounded, and their differential effects on brain and behavior are difficult to disentangle.¹⁸⁰ At the same time, enrichment paradigms are the only way to address the interactions among these factors, which are lost when attempts are made to address them in isolation. We see two ways of addressing the interpretational challenges of enrichment designs. The first is to design different types of enriched environments that systematically vary in the relative degree of inanimate versus social enrichment. The second is to gather rich behavioral data on each individual animal to arrive at individualized “lifestyle profiles” that allow researchers to classify individuals on relevant dimensions such as exploratory behavior, sociality, hierarchical status, and social clustering over time.⁹

(Continued on next page)

Box 2. Continued

- (2) *Definition of no-enrichment baselines.* Defining a no-enrichment baseline relative to enriched environments is not straightforward, due to the remarkable adaptability of mammalian species to diverse environments. For instance, standard laboratory conditions might be considered impoverished relative to the complexity of wild environments, so these studies allow limited conclusions about feral conditions. On the other hand, the laboratory mice are well adapted to their laboratory housing, such that enrichment results in departure from a new physiological baseline. Comparable intricacies arise when trying to define a baseline in the study of human living conditions.
- (3) *Automated assessment of valid behavioral indicators in animals and humans.* When studying behavior in ecologically more valid contexts, such as quasi-natural habitats, the detailed and valid classification of behavior is of key relevance. Computer vision tools permit pose estimation and behavioral analysis with greater ease, detail, and precision than manual annotation by human experimenters. For example, automated pose estimation allows detection and classification of naturalistic behaviors such as foraging, hunting, parenting, or fleeing from a predator. Deep learning algorithms can facilitate tracking multiple subjects in group settings or studying animal-object interactions.¹⁸¹ Additionally, the identification of animals' facial expressions might be helpful in categorizing responses to different types of stimuli. Dolensek and colleagues¹⁸² have shown that mice show different facial expressions in response to stimuli of varying emotional salience. It appears promising to map these facial expressions, which have been shown to represent distinct emotional states, onto corresponding human facial expressions presumably representing analogous states. The ability to track emotional states in mice is particularly valuable when trying to identify stressors in mice living in natural habitats that resemble stressors experienced by humans. Similar considerations apply for measuring everyday behavior in humans using EMA.^{131,183}

which plasticity-related microscopic changes are contributing to the macroscopic changes in mice, which in turn will help us to better understand the physiology underlying macroscopic brain changes in humans. To support the interpretation of possible structural brain changes at the macroscopic level in humans, qMRI and functional MRI (fMRI) are also administered.

Animal models of lifespan choice architectures and emergent individuality

In animal models of brain plasticity, environmental enrichment is often used to trigger and investigate plastic change.^{96–98} In the individuality paradigm of the enrichment model, a large number of animals are housed in an extensive stimulating enclosure to study how brain plasticity supports the development of individuality.⁸ Each mouse is uniquely identified by means of an implanted radio frequency identification (RFID) chip that is registered by RFID ring antennas. In this manner, researchers can track the emergence of individual differences in behavior in a shared environment.

Applying the individuality paradigm, Kempermann and colleagues found that genetically identical mice exposed to an enriched environment display different developmental trajectories, with those showing more exploration behavior also showing more neurogenesis in the dentate gyrus of the hippocampus.^{8,10} This finding corroborates the longstanding claim that behavior itself acts as a third source of individual differences in development beyond genes and environment.⁹⁹ The investigation of emerging individual differences in genetically identical mice has its human analog in the developmental study of monozygotic twins. Both in humans and animals, observations over prolonged periods of time are needed to evaluate the influences of different environmental experiences on plasticity while controlling for genetic variation.^{100–103}

Newer cage systems implementing the individuality paradigm consist of up to 70 connected standard cages⁹; see Figure 3). Given their modular architecture, these systems are ideally suited to investigate differential effects on brain plasticity as a

function of enrichment exposure at different ages and over different durations.

Environmental sources of inequality, such as differential access to learning opportunities, can be systematically introduced into the individuality paradigm at various points during ontogeny to study their immediate and lasting effects on individual differences in brain and behavior. Borrowing from concepts pioneered in behavioral economics,¹⁰⁴ researchers can use the individuality paradigm to systematically vary choice architectures at the level of the individual. The IntelliCage, a fully automated system to assess mice behaviorally,¹⁰⁵ can be used to this end. For instance, the IntelliCage can communicate with the implanted RFID chips to individually control access to learning corners that offer a range of learning tasks, assessing spatial or rule learning, for example.

How do efforts to explore environmental effects on development in rodent populations relate to longitudinal research in humans?

Human longitudinal studies of adult development have tended to neglect the effects of early environmental exposure on the developing brain.¹⁰⁶ However, an increasing number of studies have examined the effects of intra-uterine influences,^{107–109} childhood environment,^{110,111} current habitat,^{112,113} and acute as well as chronic exposure to specific aspects of the environment on the brain.^{111,114,115} One strategy has been to conduct high-density sampling of neuroimaging data within individual participants. Two examples are the MyConnectome project¹¹⁶ and the Day2-Day study.^{116–119} Such studies allow researchers to link variations in lifestyle to variations in brain parameters over time. Another strategy has been to combine ecological momentary assessment (EMA), including global position system (GPS) tracking, with a one-time assessment of brain characteristics to link real-life behavior to presumably stable neural correlates.^{120,121} Both strategies can profit considerably from the use of wearables and machine learning techniques in the acquisition and analysis of day-to-day behavior.¹²²

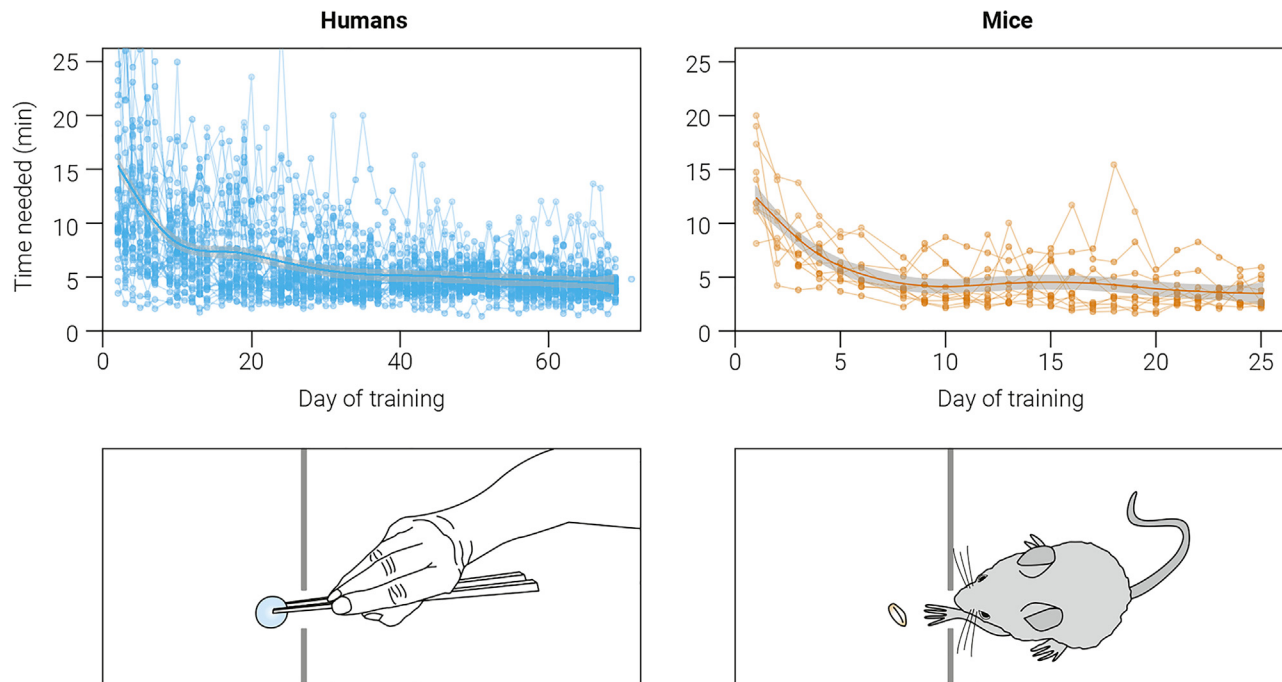


Figure 2. Coordinated skill-acquisition studies across species

Mice and humans train a fine motor skill over several days. In mice, the well-established single-pellet reaching task is used.⁹⁴ Humans are asked to grasp irregularly shaped food items (M&Ms) using chopsticks. Learning curves are similar across species (preliminary study data, dissertation M.H.).

Human studies of this sort can be aligned with animal models that vary factors present in both animal and human ecologies with greater experimental control to attain more precise insights into the age-graded effects of various environmental exposures on behavior and subsequent development. This strand of research also directs conceptual attention to the question of what it is exactly that constitutes an enriched environment in different species,^{14,123} including humans,¹²⁴ and to what extent active engagement with this environment is necessary, or passive exposure sufficient, to shape brains across ontogeny.¹²⁵

Comparing humans to animals in low-constraint settings

Recent years have seen an upsurge in the investigation of freely behaving animals, including the search for tasks and stimuli that are based on their natural living environments. Such attempts at ecological validity and equivalence move research with animals closer toward human research that seeks to relate individual differences in lifestyles to individual differences in brain, behavior, and health.^{116–118} Larger and more natural housing conditions for animals are required for such experiments. For instance, mice can be housed and studied in large outdoor vivariums that afford more complex and naturalistic lifestyles.¹²⁶ Such semi-natural outdoor enclosures maximize ecological realism by providing many social partners, high physical complexity, and a semi-natural ecosystem. At the same time, relatively high levels of experimental control can be maintained.¹²⁷ More naturalistic environments have proven to be suitable for laboratory mice and to increase animal welfare.^{128,129} Environmental heterogenization instead of standardization also promises to

overcome conflicting test outcomes, improve external validity, and increase reproducibility.¹³⁰

More natural housing conditions set the stage to investigate the behavioral repertoire of a given species differently than when held in the laboratory. For example, re-wilded mice probably show different behaviors like foraging or digging and experience stress differently than laboratory mice. We might imagine studying mice in their more natural environments in ways that are similar to EMA in humans,¹³¹ and vice versa. For instance, a study on real-world experiential diversity among young adults¹²⁰ used “roaming entropy” as a measure of spatial exploration. This measure has originally been developed to track the emergence of individual differences in spatial exploration among rodents living in enriched environments⁸; see Figure 4. In coordinated across-species investigations, one would be able to experimentally introduce species-adequate stressors and observe individuals’ responses to them. Such investigations can be augmented by longitudinal brain imaging and non-invasive or mildly invasive deep phenotyping to assess the dynamic development of plastic changes in brain structure, brain function, and behavior.

COMPONENT 3: TOWARD THEORIES AND MODELS OF PLASTIC CHANGE THAT INTEGRATE SCALES OF MEASUREMENT

To facilitate theory building and generalization, the interchange between animal models and human research needs to be informed by theories and models that explicitly seek to bridge the gap between microscopic and macroscopic observations.⁴ These models and theories need to be embedded into conceptual

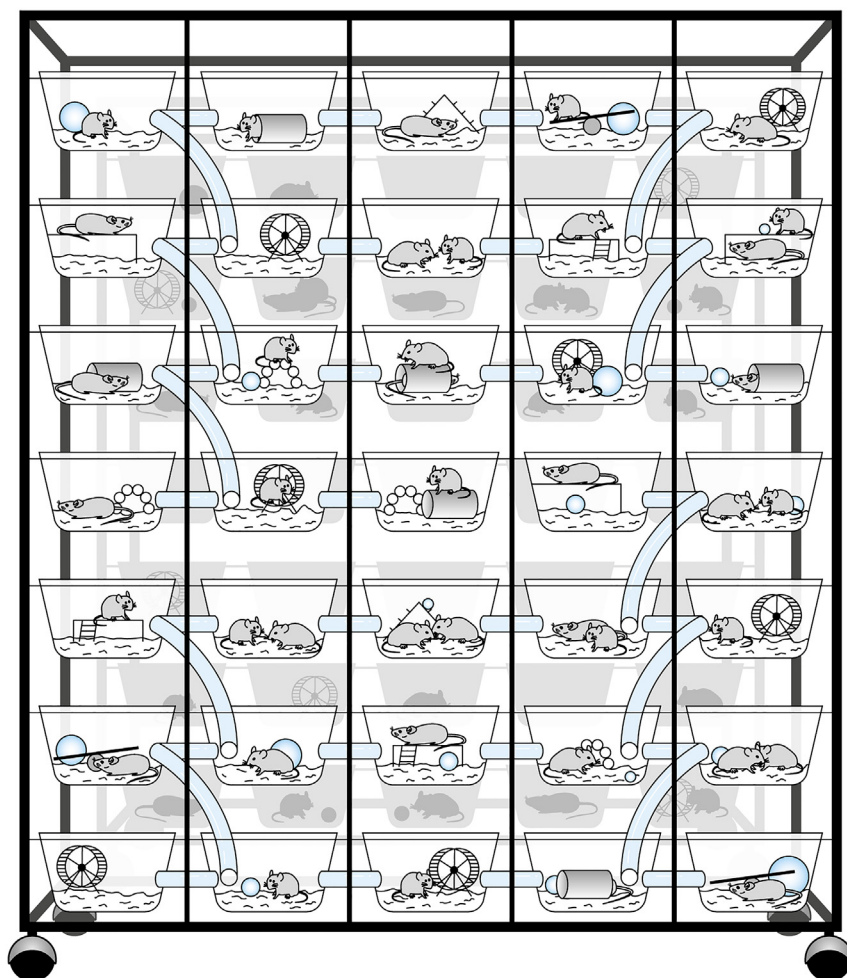


Figure 3. Display of the cage design used in the individuality paradigm⁹

Multiple standard cages are connected to each other with connector tubes that are equipped with RFID antennas to track mouse movements. The standard cages can be equipped with a large variety of environmental affordances and opportunities. Given that the mice are individually tracked, experiences can be experimentally manipulated at the individual level in the course of development.

and cellular mechanisms that enable the storage and reactivation of learned information in the brain. Recent advances in the development of engram labeling methodologies have proven particularly useful in this regard.¹⁴⁰

Second, bridge models need to specify how microscopic changes, such as the ones posited by Frank et al.,¹³⁹ map onto macroscopic observations. The empirical basis for such mapping functions needs to be established by the kind of empirical work described above. To the extent that we can establish empirical connections between microscopic and macroscopic levels of measurement, we can predict and interpret macroscopic changes observable in humans on the basis of microscopic observations made in animal studies.

Motor skill acquisition in rodents and humans as a testbed for theory development

One initial step toward linking microscopic and macroscopic levels is the “expansion-

frameworks that delineate the ontogenetic role and environmental contexts of plastic change.^{4,5,73,74,132–134} Specifically, there is a need to build models that map what is observable in humans onto what can be studied in animals and vice versa. This requires conceptual integration across scales of measurement, space, and time. For instance, models of this type would specify the ways in which nonlinear gross volume changes observed with sMRI reflect changes in dendritic sprouting,¹³⁵ myelination, or a number of other parameters that might result in volume changes.

Such integrative bridge models are characterized by two key features. First, they need to model the dynamics of plastic change at the microscopic level. For example, extant models of plastic change posit that new dendritic spines form clusters during learning.¹³⁶ Experimental studies have corroborated that dendritic spine clustering can indeed be observed in animals, for example, in response to motor learning.¹³⁷ Some computational models have implemented clustered structural plasticity and explored ensuing network dynamics.^{138,139} As an example, in a biophysically inspired model, Frank et al.¹³⁹ found that dendritic spine turnover before a learning phase was a driving mechanism for the clustering of spines in response to learning. This work also includes the identification of molecular

exploration-selection-refinement” (EESR) theory of brain plasticity.^{4,6} The theory has been developed to capture plastic changes during skill acquisition, with an emphasis on motor skills. In the following, we review some of the empirical evidence that has informed the formulation of the theory and present its core predictions.^{4,6}

Studies of rodents have shown that cortical representations of limbs and movements initially expand^{141,142} and then renormalize during learning.¹⁴³ Importantly, these studies have found that trial-to-trial variability of local brain activity patterns is larger earlier than it is later in learning. According to EESR theory, this finding suggests that a variety of different circuits of excitatory neurons within the motor cortex are tried out early in learning, whereas performance later in learning reflects the stabilized use of a specific neural circuit devoted to the task.¹⁴⁴ The early trial-to-trial variability of activity patterns has been proposed to signify exploration of possible network states,^{145,146} in the sense that initial variability may provide a pool of circuits from which the optimal one can be selected through system-level feedback mechanisms, such as striatum-mediated reinforcement learning or cerebellum-based sensory prediction errors.^{146–149}

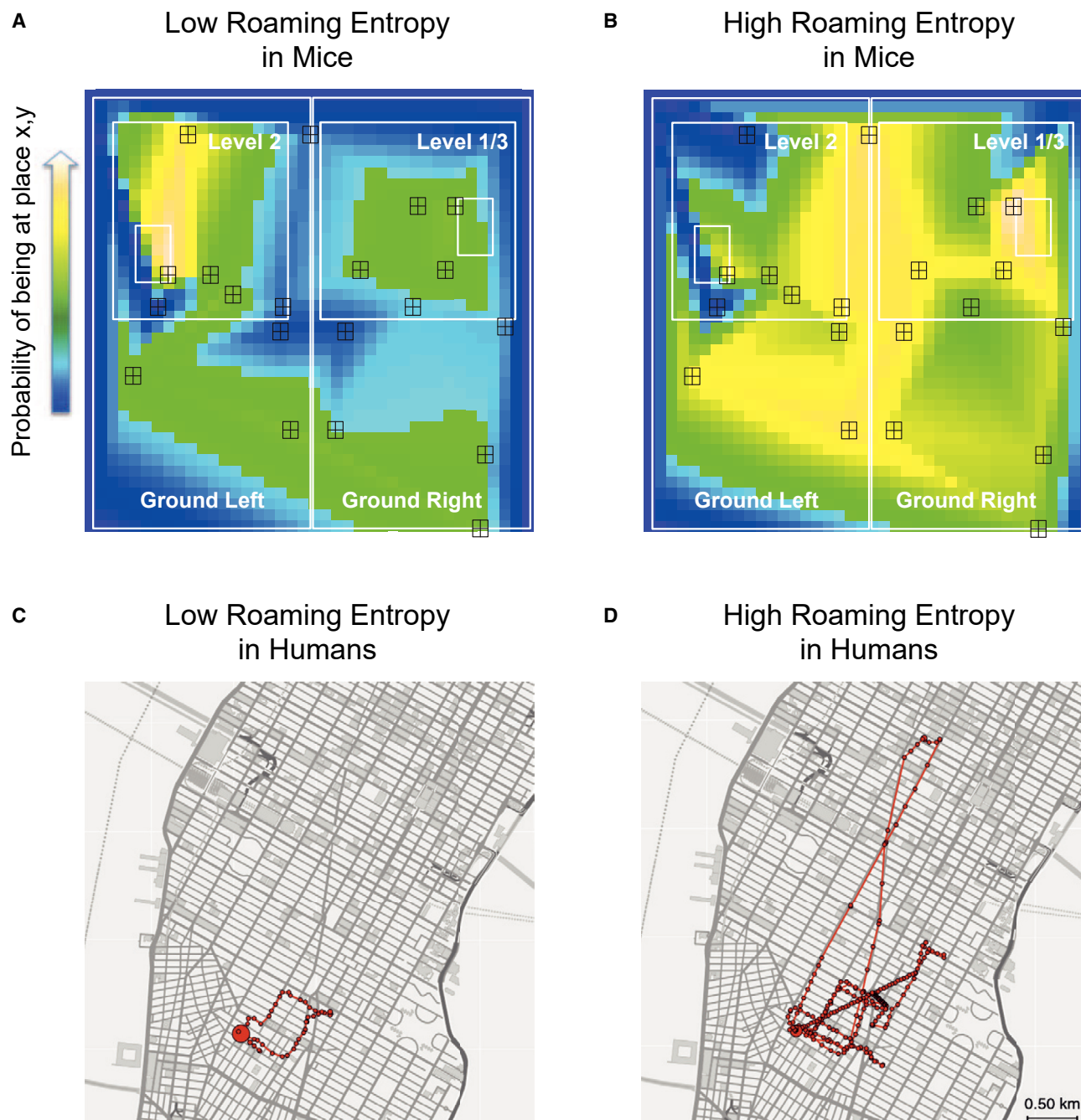


Figure 4. Quantifying spatial coverage across species using the measure of roaming entropy

Roaming entropy is at a minimum when an individual remains at the same place during a given time period and large when an individual spends equal amounts of time at many different places; for details, see Freund et al.⁸ In mice,⁸ individual differences in cumulative roaming entropy, indicating the active coverage of territory, have been found to correlate positively with individual differences in adult hippocampal neurogenesis. (A) and (B) show an animal with low versus high roaming entropy, respectively. In humans,¹²⁰ greater roaming entropy on a given day has been found to be associated with more positive affect on that same day within individuals; this effect was stronger for individuals who exhibited greater functional coupling between hippocampus and striatum. (C) and (D) show a research participant living in New York City on a day with low versus high roaming entropy, respectively.

Changes in brain activity related to skill learning eventually trigger changes in structure. For example, synaptic density in the rodent motor cortex initially increases and then decreases during learning.¹³⁷ Novel synapses rapidly form in the motor cor-

tex of rodents during motor learning.^{137,150,151} With continued training, the growth of dendritic spines (a proxy for synapses) is followed by stabilization of the new spines and removal of old spines, and overall spine density almost reverts to

pre-training levels.^{47,94,152} This kind of synaptic remodeling occurs both in deep⁹⁴ and superficial¹⁴⁴ layers of the motor cortex. The probabilities of deletion of old synapses and formation of new ones are typically thought of as locally governed by the rules of Hebbian and homeostatic plasticity.¹⁴⁷

Interestingly, recent studies of learning-related changes in human brain structure also show increases followed by renormalization. Using sMRI, several researchers have observed experience-dependent increases and decreases in regional estimates of human brain volume and cortical thickness in adulthood.^{53,153–156} For instance, Wenger and colleagues¹⁵⁴ acquired 18 T1-weighted structural MR images over a 7-week period for each of 15 right-handed adult participants who practiced left-handed writing and drawing during that time. After 4 weeks, increases in gray-matter probabilities were observed in both left and right primary motor cortices relative to a control group; however, 3 weeks later, these differences were no longer reliable. Time-series analyses showed that estimates in gray-matter probabilities in primary motor cortices increased during the first 4 weeks of learning to write and draw with the left hand and then partially renormalized during continued practice.

The EESR theory of plastic change

Based on this evidence, Lövdén and Lindenberger have proposed the EESR theory of plastic change during skill acquisition^{4,6} (for related considerations, see previously published studies^{147,149,157–159}). Figure 5 presents a summary description of EESR theory. Driven by a large mismatch between the expected goal behavior and its actual execution, a task-relevant cortical area expands and is subsequently explored for neural circuits that can approximate the goal behavior. During this exploration, different actions are probed and different behavioral patterns to achieve the same goal are tested. Trial-to-trial behavioral variability and variability of neural activity patterns are therefore large. This broad activity in turn induces structural brain changes, such as the formation of synapses. Which signals exactly trigger dendritic spine formation is not yet clear. In addition to dopaminergic modulatory signaling mediating the reinforcement of actions, γ -aminobutyric acid (GABA) signaling is likely to play an important role in the initial stages of neuroplastic transformation, as evidenced by observed reductions in GABA concentration within primary sensorimotor cortex in motor sequence learning tasks.¹⁶⁰ The shift in excitatory-inhibitory (E/I) balance toward excitation may trigger a plastic state that favors initial expansion and subsequent exploration and is reminiscent of the regulation of critical periods by maturing GABAergic parvalbumin-positive inhibitory neurons in early childhood.^{133,161,162}

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. In other words, another class of signals is needed to trigger the end of exploration and the subsequent stabilization of representations during the refinement of skill acquisition. In ontogeny, the formation of perineuronal nets is critical for closing critical periods.^{133,162} Perineuronal nets may also help to stabilize the neural substrate of skilled performance,

with the ensuing retraction of structure and decreases in neural activity. After circuit selection, neural activity as well as neural and behavioral variability decrease. Synaptic remodeling in the selected neural circuit continues to occur in a subsequent repetition-based refinement of task execution, but both novel and pre-existing structures in unselected circuits retract.

Lindenberger and Lövdén^{4,6} hypothesize that the EESR sequence is reflected at the macroscopic level by several indicators. First, task-related activation as measured by fMRI blood-oxygen-level-dependent (BOLD) signal in task-relevant regions is assumed to be high during early phases of skill acquisition, as different and presumably inefficient task representations are being probed, and to decrease with increasing task proficiency, resulting in a monotonically decreasing function. Second, they hypothesize that three macroscopic indicators follow an inverted U-shape function: (1) E/I balance, as measured by MRS, tracking the opening and closing of the plastic episode; (2) synaptic density, as measured by PET, tracking synapse formation and elimination; and (3) regional brain volume as measured by sMRI (e.g., VBM), tracking the tissue expansion and renormalization. Third, as the skill approaches asymptotic levels and competing neural ensembles have been eliminated, they expect that the neural ensemble executing the task stabilizes, indicating the selection and refinement of the underlying engram.¹⁶³ Therefore, the self-similarity of task representations as measured by fMRI-based or EEG-based representational similarity analysis (RSA) is expected to increase in the course of skill acquisition.¹⁶⁴

Clearly, the microscopic-macroscopic mapping functions hypothesized by EESR theory need to be corroborated by empirical evidence. In some cases, such mappings might not be straightforward or even possible; for instance, overall changes in regional brain volume may represent the net outcome of many different microscopic processes that cannot be separated in the aggregate. At the same time, better specificity and resolution of MRI methods, including MRS, and improvements in PET imaging may soon facilitate the physiological interpretation of macroscopic measures and inform attempts to build models and theories that connect microscopic and macroscopic levels of analysis.

OUTLOOK

To better understand plasticity in humans, its study must be coordinated and integrated across species and scales of measurement. In this article, we have showcased several opportunities for improved coordination and integration. We acknowledge that many more opportunities exist and that our exposition was exemplary rather than exhaustive. To explore and exploit all of these opportunities, we need to intensify the dialogue between researchers who study plasticity in animals and researchers who investigate plasticity in humans and to substantiate the results of this dialogue by developing models and theories that connect microscopic and macroscopic scales of measurement. Engagement in this dialogue will transform experimental paradigms and research questions on either side and yield new insights into the nature of plastic change. A good example for such collaboration concerns the

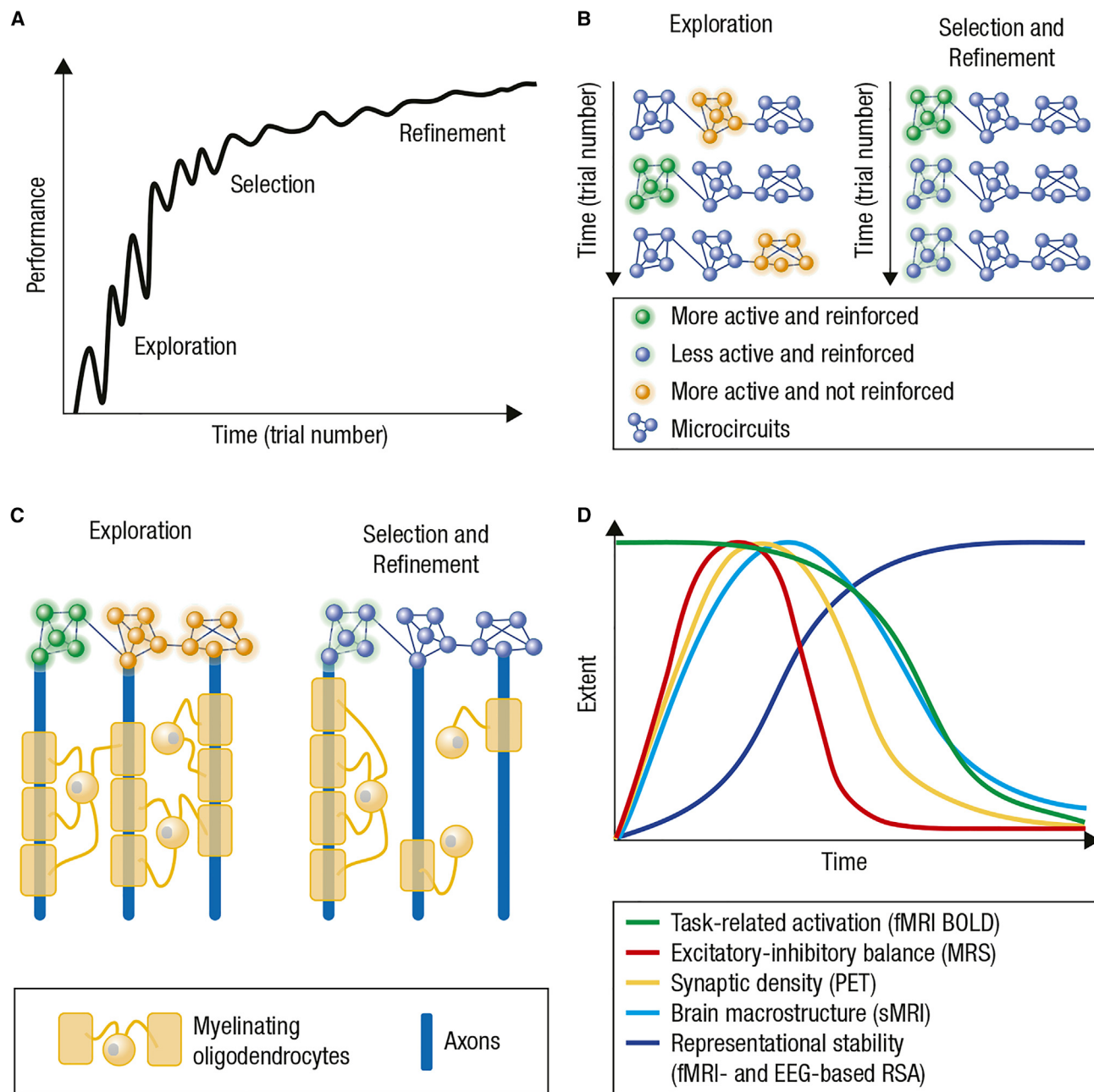


Figure 5. The EESR theory of local plastic change

According to the theory, local plastic change proceeds in three phases that together form a learning cycle. During the initial stages of expansion and exploration, when available or new microcircuits that can execute the task are being probed, there is substantial trial-to-trial variability in (A) behavior and (B) patterns of neural activity. 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 (C). Eventually, the best-performing microcircuit is selected, and neural and behavioral variability starts to decrease (A and B). In a subsequent refinement stage, processing in the selected microcircuit stabilizes through further structural refinement while novel structures of unselected microcircuits continue to retract (C). At the macroscopic scale, expansion-exploration-selection-refinement (EESR) theory predicts: (1) a decrease in functional activation as measured by fMRI BOLD; (2) sequentially ordered inverted U-shape functions for E/I balance measured by MRS, synaptic density measured by PET, and brain volume measured by sMRI; (3) a late-evolving monotonic increase in the self-similarity of neural activation patterns corresponding to a specific behavior or percept as measured by fMRI-based or EEG-based representational similarity analysis (RSA) (D). Modified after Lindenberg and Lövdén.⁴

phenomenon of “infantile amnesia,” where attempts are underway to link human longitudinal data to animal experimentation.^{165–167}

This dialogue is not without challenges, both institutionally and for individual researchers. For instance, researchers with an interest in human skill acquisition are called upon to enhance the mechanistic interpretability of their imaging and behavioral data by aligning their experimental paradigms more closely to existing animal paradigms, which raises the issue of ethological validity. Researchers who study the epigenetic emergence of individual differences in animals are invited to ask themselves how their research can help to understand the developmental origins of individuality in humans, including notions of agency and free will.^{8,99,168} Researchers studying the human lifespan are asked to come up with paradigms that simulate their research questions, such as unequal access to learning opportunities, in animal populations.

Organizationally, research on plasticity in animals and humans is often performed at different institutes, departments, and laboratories. Also, with some notable exceptions, funding schemes are typically geared toward one or the other branch of research but rarely at their integration. We hope that this article helps to encourage institutions and funders to place greater emphasis on the coordination and integration of research on plasticity in animals and humans.

ACKNOWLEDGMENTS

The plan to write this article can be traced back to the Invited Conference, “Understanding Neural Plasticity: From Animal Models to Human Individuality,” which was held September 4–10, 2022, at Ringberg Castle, Germany (organizers: T.B., S.K., and U.L.). The authors thank Martin Lövdén, Warsha Barde, Claudia Buss, Pico Caroni, Mallar Chakravarty, Claudia Clopath, Geoffroy Delamare, Kristen Delevich, Jörn Diedrichsen, Manfred Gahr, Adam Hantman, Takao Hensch, Mark Hübener, Agnieszka Kulesza, Jason Lerch, Ju Lu, Andreas Lüthi, Ania Majewska, Nora Moog, Miriam Mosing, Iris Odstrcil, Amos Pagin, Tomás Paus, Tomás Ryan, Constance Scharff, Maria Spolidoro, Tibor Stark, Fredrik Ullén, Daniela Vallentin, Daniel Vosberg, Elisabeth Wenger, Linda Wilbrecht, Robert Zatorre, Sara Zocher, and Yi Zuo for productive discussions at the conference. We also thank Julia Delius for editorial assistance and helpful comments on an earlier version of this manuscript. M.H. was a predoctoral fellow of the International Max Planck Research School on the Life Course (IMPRS LIFE; www.imprs-life.mpg.de) during work on this article.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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