Neuroplasticity

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Abstract

Our genetic code cannot specify every single connection between individual nerve cells. Hence, every brain has to start as a relatively structureless but extremely flexible network of nerve cells that has the ability to "wire" itself exactly in the way in which it is best adjusting to its individual environment with its unique requirements. Neuroplasticity denotes this inherent ability of the brain to adapt with macro-scale changes in response to altered environmental demands (Lövdén, Bäckman, *et al.*, 2010). It is therefore an adaptive process triggered by a prolonged mismatch between the functional supply the brain can momentarily provide and the experienced demands the environment currently poses. In this chapter, we first review the accumulated evidence on neuroplasticity, both in animal and human literature. We then turn to biological underpinnings potentially underlying the detectable changes in gray matter structure as visible on magnetic resonance (MR) images. Finally, we review evidence on the sequential progression of structural changes, which has revealed a pattern of expansion followed by renormalization and reiterate the importance of paying close attention to the complex nature of plastic changes.

Introduction

The massive amount of connections between neurons cannot be simply inscribed in our genetic code, as the former severely outnumbers the latter. Amongst others, our DNA is assigned to the important task of encoding the variety of nerve cell forms and different neurotransmitters, but it cannot specify the exact connections between individual neurons. Hence, every brain has to start as a relatively structureless, but extremely flexible network of nerve cells that has the inherent ability to "wire" itself exactly in the way in which it is best adjusting to its individual environment with its unique requirements. Plasticity is therefore an intrinsic property of the human brain and constitutes evolution's invention to enable the nervous system to escape the restrictions of its own genome and adapt to environmental pressures, physiologic changes, and experiences (Pascual-Leone *et al.*, 2005). Conceivably, there are also quite obvious, definitely indispensable limits to how plastic a brain can be. It has to be stable too, to remain operational and keep and store functions once learned. Plastic changes are also metabolically costly (Kuzawa *et al.*, 2014), a circumstance that becomes increasingly important in systems that have slowly started to accumulate damage (as in aging) and may therefore have literally nothing to spare. So at best, there is a balance between stability and neuroplasticity that results in a brain that is both solid and reliable where it can be, and capable of adaption where it has to be.

The concept of plasticity

In the definition we subscribe to, neuroplasticity denotes the inherent ability of the brain to adapt with macro-scale changes in response to altered environmental demands (Lövdén, Bäckman, *et al.*, 2010). Within this framework, plasticity is an adaptive process triggered by a prolonged mismatch between the functional supply the brain can momentarily provide and the

experienced demands the environment currently poses, as for example when a new cognitive task needs to be accomplished.

In the majority of cases, the brain can meet requirements posed by its environment through neuronal and behavioral variability and flexibility, that is, by optimizing its performance within a given state of resources and using the existing functional repertoire. However, if these processes of flexibility within a given state do not suffice in fulfilling environmental demands – either due to dramatic changes in requirements or due to damaged functionality of the brain following brain injury – then more fundamental change is demanded and can manifest in the form of plasticity (Lövdén, Bäckman, *et al.*, 2010). We have previously raised the notion that flexibility and plasticity may follow different contrary trajectories across the lifespan: While plasticity is highest in childhood and decreases towards old age, flexibility increases from childhood on, peaks in young adulthood, and decreases thereafter (Kühn and Lindenberger, 2016).

Evidence for neuroplasticity in the context of cognitive training

In the 1960's and 70's, it was the obligatory animal research providing indications for changes of cortical patterns and brain structure as a concequence of altered environmental circumstances or experiences. It was firmly established that enriched environments can lead to changes in brain weight (Rosenzweig, Bennett and Krech, 1964), and cortical thickness (Rosenzweig, Bennett and Diamond, 1972). Rats trained in a motor skill task showed increased dendritic branching in the motor cortex (Withers and Greenough, 1989) and an increased number of synapses per neuron in the cerebellar cortex (Black *et al.*, 1990).

Altman was the first to report even new neurons and neuroblasts in adult rats (Altman, 1962), while Kaplan corroborated these results and also found evidence that complex environments could stimulate neurogenesis in adult visual cortex (Kaplan and Hinds, 1977). With the important work by Gould and colleagues who demonstrated adult hippocampal

neurogenesis also in mammals that are more related to humans (Gould, Reeves, *et al.*, 1999), adult mammalian neurogenesis is now firmly established and has been shown to be involved in learning (Gould, Beylin, *et al.*, 1999). In rodents, environmental enrichment and voluntary exercise have been shown to enhance neurogenesis (Kempermann, Kuhn and Gage, 1997; van Praag, Kempermann and Gage, 1999).

For a long time, it was assumed that brain structure was malleable and amicable to influences from the outside only during critical periods in early life, and to be absent thereafter. And indeed animal models have suggested that age limits the capacity for adaptive changes: The aged rat brain has been found to respond more slowly and to a lesser extent to chemically-induced seizures, suggesting a more stable system (Wagner *et al.*, 2000). Especially changes in thin spine morphology have been amongst possible candidate mechanisms potentially responsible for age-related impairments in learning (Dumitriu *et al.*, 2010). Bloss and colleagues (2011) reported an experiment using the negative impact of stress on dendritic spines to demonstrate plastic changes in different age groups. In young rats, stress resulted in dendritic spine loss and altered patterns of spine morphology. In contrast, spines from middle-aged and older animals were remarkably stable and did not show evidence of remodeling. The data provide evidence that experience-dependent spine plasticity is altered by aging and, together with other literature on age differences in plastic responses, support a model in which dendritic spines become progressively less plastic and more stable in the aging brain (Grutzendler, Kasthuri and Gan, 2002; Holtmaat and Svoboda, 2009; Bloss *et al.*, 2011).

Nevertheless, it has been shown repeatedly that neuroplasticity can take place in the adult brain as well. Animal data show cognitive benefits and neural reorganization in rodents, after long-term voluntary exercise in running wheels (van Praag, Kempermann and Gage, 2000) and training periods on a treadmill (Aguiar *et al.*, 2011), to name only two examples. In addition to exercise, enrichment of the environment has also been shown to evoke changes in

dendrites in middle-aged rats (Green, Greenough and Schlumpf, 1983) and in spiny branchlets of cerebellar Purkinje neurons in aged rats (Greenough *et al.*, 1986). Enriched housing can even return the number of cells of older animals to the level of younger animals living in impoverished cages (Kolb *et al.*, 1998).

These original findings elicited hope for similar effects in humans. Given that it is not possible to measure human brain structure *in-vitro* in healthy, living individuals, advances in non-invasive magnetic resonance imaging (MRI) have opened up new windows into the investigation of changes in the human brain's macrostructure. MRI uses a strong magnetic field to align hydrogen atoms of water molecules in tissue, and radio frequency fields to systematically change this alignment (Huettel, Song and McCarthy, 2004). This magnetization results in a rotating magnetic field created by the hydrogen atoms as they return to baseline which can be detected by the MR scanner. The emerging signal can then be used to construct an image of the brain because different tissues have different magnetic properties. On the resulting anatomical images one can then differentiate between gray matter, white matter, and cerebrospinal fluid, which can be quantified in terms of volume by means of manual tracing or automatic segmentation. Even though, conceivably, *in vivo* MRI cannot inform us at the same detailed cellular level as methods in animal research can, it still offers a unique window into brain changes on the macrostructural level.

In the last years, several studies have devoted themselves to investigating instances of neuroplasticity and have identified situations in which plastic changes were observable. Maguire and colleagues (Maguire *et al.*, 2000; Maguire, Woollett and Spiers, 2006) have found an enlarged region in posterior hippocampus in London taxi drivers in contrast to bus drivers and have observed an enlargement of the same region in the course of becoming a licensed taxi driver, while acquiring London's complex street layout (Woollett and Maguire, 2011). Further evidence for changes in gray matter in reponse to experience comes from musicians (Gaser and Schlaug, 2003; see also Swaminathan and Schellenberge this volume),

professional typists (Cannonieri *et al.*, 2007), and medical students preparing for their final exam (Draganski *et al.*, 2006). Also, learning how to juggle for three months has been shown to elicit temporary expansion in temporal lobe and intraparietal sulcus, both in younger (Draganski *et al.*, 2004) as well as in older adults (Boyke *et al.*, 2008), and practicing two weeks of mirror reading has led to reduced activation alongside with an increased volume of gray matter in occipital lobe (Ilg *et al.*, 2008). Eight weeks of memory training using the Method of Loci induced cortical thickness changes in middle-aged and elderly healthy volunteers (Engvig *et al.*, 2010; see also Wenger *et al.* this volume). 100 days of cognitive training have been shown to evoke plastic changes in white matter in corpus callosum (Lövdén, Bodammer, *et al.*, 2010) and spatial navigation training has led to a deceleration of typical age-related decline in hippocampal volume (Lövdén *et al.*, 2012), as well as to cortical thickening in precuneus und paracentral lobule in younger adults (Wenger *et al.*, 2012). Also playing a video game that involves navigating in 3D-space has been shown to lead to changes in the right hippocampal formation (Kühn *et al.*, 2014; see also Green *et al.,* Strobach and Schubert this volume). Mårtensson and colleagues (2012) studied changes in brain structure following three months of intense foreign-language acquisition. Results showed increases in hippocampal volume and in cortical thickness in left middle frontal gyrus, inferior frontal gyrus, and superior temporal gyrus for military interpreters compared to a control group, whereby some of these regions showed a correlation with behavioral measures of proficiency or struggeling. Last but not least, physical exercise has been identified as a powerful agent to influence also adult human brain structure (see also Pothier and Bherer this volume): it has been shown that hippocampus size increased after one year of moderate-intensity exercise training (Erickson *et al.*, 2011) and cerebral blood volume – an indicator of exercise-induced neurogenesis – in dentate gyrus increased after three months of exercising (Pereira *et al.*, 2007). Changes in fitness have been associated with changes in hippocampal perfusion and volume of the hippocampal head in the context of a three-month fitness intervention program

(Maass *et al.*, 2015) and with changes in hippocampal microstructure, pointing to a more dense tissue, after six months of ergometer training (Kleemeyer *et al.*, 2015).

Taken together, a considerable number of studies investigating experience-dependent macrostructural changes in human gray matter have accumulated over the last say 20 years (for comprehensive reviews, see May, 2011; Zatorre, Fields and Johansen-Berg, 2012; Lövdén *et al.*, 2013). However, some of these studies do not offer optimal grounds for indisputable conclusions but suffer from various flaws, in both study design as well as statistical analysis regards (Thomas and Baker, 2013; see also Cochrane *et al.,* Schmiedek this volume). Some of these studies for example lack an appropriate control group against which the results in the experimental group could be compared. This seems especially important in study designs with only two measurement time points where scanner drifts or normal "variability" in brain structure as visible on MR images are hard to distinguish from true effects. Also, so far it seems impossible to state ubiquitously whether experience-dependent brain changes are or are not reduced in aging. With only a few exceptions, there is generally a lack of age-comparative studies that investigate both younger and older adults with the same training paradigm. It remains hard to gauge to which extent the aged brain harbors the potential to exhibit plastic changes relative to a younger brain. More studies using samples with a wide age range or at least two or three age groups plus appropriate control groups are warranted to further explore the premises that need to be fulfilled in different brain regions (e.g., hippocampus vs. cortical regions) within aging brains to set grounds for arising plastic changes.

Microstructural processes underlying changes in gray matter

With respect to underlying biological mechanisms, MRI findings do not provide clear evidence on cellular and molecular mechanisms of changes in gray matter. Moreover, phenomena visible with MRI are most likely never the result of a single process happening

independently. Instead, they are rather a result of many coordinated structural changes involving various cell types. Candidate mechanisms possibly underlying the visible changes on T_1-weighted images are neurogenesis, synaptogenesis, changes in neuronal morphology, axon sprouting, dendritic branching, glial changes, or angiogenesis (for a summary of possible biological processes see also Zatorre, Fields and Johansen-Berg, 2012). In the following, we will briefly summarize knowledge on these biological mechanisms.

Neurogenesis denotes the growth of new neurons and has repeatedly been demonstrated in the hippocampus of adult rats, living in an enriched environment (e.g., Kempermann, Gast and Gage, 2002; Kronenberg *et al.*, 2006). As monthly newly produced cells make up only a small part of the total number of hippocampal neurons, neurogenesis is likely a minor factor contributing to changes visible with MRI. Changes observed outside of the hippocampus are probably not due to neurogenesis, as growth of new neurons in adults has only been established in the dentate gyrus and the olfactory bulb (e.g., Ehninger and Kempermann, 2008; Huart, Rombaux and Hummel, 2013) and, more recently, in humans in the striatum (Ernst *et al.*, 2014). Whether neurogenesis in the neocortex can occur later in life is still highly controversial (Rakic, 2002; Tan and Shi, 2013).

Another candidate biological process persumably contributing to MRI volume increases is gliogenesis, referring to an increase in the number of non-neuronal cells (including oligodendrocytes, astrocytes, microglia, and ependymal cells). Glia cells maintain ion homeostasis, regulate blood flow in response to neuronal activity, form myelin, and provide support and protection for neurons (Wang, Takano and Needergaard, 2009; Brodal, 2010). Glial cells are highly plastic and display a number of morphological changes in response to altered experience, including increased cell number, volume fraction, increased cell surface, and proliferation of their processes (Sirevaag and Greenough, 1991; Dong and Greenough, 2004). Glial processes could in theory increase to support new synapses, or to compensate for neuronal process loss (Anderson, 2011). Thus, increases in gliogenesis could

to some extent underlie gray matter changes observed with MRI (Zatorre, Fields and Johansen-Berg, 2012).

Besides neurogenesis and gliogenesis, synaptogenesis and changes in spine morphology have been discussed in the context of learning and gray matter alterations. In animal work, synapse formation has been implicated in supporting learning-dependent changes in cortical function (Kleim *et al.*, 2002; Trachtenberg *et al.*, 2002). Changes in dendritic length and branching or in the actual number of dendritic spines per neuron are likely to contribute to experience-dependent volumetric changes in gray matter (e.g., Kolb, Cioe and Comeau, 2008; Holtmaat and Svoboda, 2009; Fu and Zuo, 2011). Additionally, angiogenesis, that is, changes in vasculature, is likely to appear following especially exercise-training (Swain *et al.*, 2003). These changes could support increased energy demands of new or changed neural tissue via a growth of capillaries.

Overall, the bulk of evidence suggests that experience-dependent neuroplasticity may be to a large extent mediated by synaptogenesis (Black *et al.*, 1990; Kleim *et al.*, 2002), changes in dendritic spines/dendritic branching (Trachtenberg *et al.*, 2002; Holtmaat and Svoboda, 2009), and changes in non-neural cells like glia (Dong and Greenough, 2004). As glia process growth and retraction in response to manipulations are in general complicated, they might cloud direct relationships between synapse numbers and regional volume (Anderson *et al.*, 1994).

Since the early publications reporting experience-dependent gray matter changes in humans (e.g., Amunts *et al.*, 1997; Maguire *et al.*, 2000; Draganski *et al.*, 2004), speculations about the microstructural biological correlates of these effects have filled paragraphs and paragraphs of countless discussion sections. A future challenge remains the identification of cellular changes underlying the macrostructural changes currently observed with MRI. Meeting this challenge requires employing continuously newly developed MR sequences (Tardif *et al.*, 2016), greater cross-talk between those studying human populations and those

working with animals, as well as a greater integration of techniques. This has for example been done in a study by Sagi and colleagues (2012), where they used diffusion-tensor imaging to investigate changes in the hippocampus in humans following a spatial learning and memory task. They found a significant reduction of mean diffusivity (MD) in hippocampus and parahippocampus after only two hours of training that correlated with behavioral improvement. Additionally, they conducted a supporting rat study with a short-term water maze task to investigate "equivalent" changes on a more detailed microstructural level in the animal brain. Histological analysis of the rat brains indicated that within the regions of MD decrease there was an increase in the number of synaptic vesicles, astrocytic activation, and an increase in BDNF expression (Sagi *et al.*, 2012). Another study focusing on the neural correlates of MRI volume changes found neurogenesis to be the best marker explaining hippocampal gray matter volume after voluntary wheel running in mice (Biedermann *et al.*, 2016). In this study, they compared a group of running mice to sedentary ones, acquired a typically used anatomical MR image and sacrificed the animals immediately after to perform histological analyses. Besides newborn neurons, they also investigated glial cells, microglia, proliferating and pyknotic cells, neuronal activation, blood vessel density and arborization. Interestingly, none of the other above mentioned cell types showed a clear correlation pattern with MR volume changes, even though a marker for astrocytes also showed a significant difference between the two groups (Biedermann *et al.*, 2016). Yet another study by Lerch and colleagues investigated mice trained on different versions of the Morris water maze task (Lerch *et al.*, 2011). Using high resolution MRI, they showed specific volume changes in the hippocampus in mice trained on a spatial variant of the maze, and changes in the striatum after the cued version of the maze. Subsequent immunohistochemistry revealed a correlation between volume increases and a marker for neuronal process remodeling but not with neurogenesis, neuron or astrocyte numbers or sizes (Lerch *et al.*, 2011). Such studies that discuss the biological correlates of structural MR measures, together with advances in MR

image acquisition (Hamaide, De Groof and Van der Linden, 2016; Lerch *et al.*, 2017) will continue to enable key insights into how neuroplastic changes are implemented.

Time course of plastic changes

As reviewed above, structural brain changes have been observed following many different kinds of skill acquisition and learning. Plastic changes might even emerge much faster than described in the aforementioned studies: Gray matter alterations have been reported after only two weeks of mirror reading training (Ilg *et al.*, 2008), one week of juggling training (Driemeyer *et al.*, 2008), one week of daily pain stimulation (Teutsch *et al.*, 2008), five days of repetitive transcranial magnetic stimulation (May *et al.*, 2007; see also Holes *et al.* this volume), and three days of practicing signature writing (Hamzei *et al.*, 2012). Even two sessions of practice in a complex whole-body balancing task (Taubert *et al.*, 2010), two hours (spread out over three days) of learning subcategories of colour names (Kwok *et al.*, 2011) or passive viewing of pictures during 263 seconds (Månsson *et al.*, 2019) have led to reports on gray matter alterations.

Many of these studies make use of the classic design, measuring gray matter structure before and after the introduction of a novel experience. It is therefore implicitly assumed that structure is, if at all, developing monotonically during the intervention or training phase. Related work in animals, however, shows initial increases in structure in the beginning of training that are then followed by partial or complete renormalization as experience continues (Dupret *et al.*, 2007; Quallo *et al.*, 2009; Xu *et al.*, 2009; Reed *et al.*, 2011). Quallo and colleagues (2009) analyzed structural data of three adult macaque monkeys, collected on multiple occasions before, during, and after learning to use a rake to retrieve food. They found learning-related increases in task-relevant brain regions, which also mapped onto the learning curves. Crucially, despite continued training, the observed increased gray matter structure decreased again after the monkey's performance reached asymptote. After training, the

volume was still enlarged as compared to before training, but much smaller in magnitude than the peak effect observed before asymptotic performance was reached. Molina-Luna and colleagues (2008) trained rats to perfom a skilled reaching task and found expanded cortical maps after three days of training. After eight days of training, however, these expansions subsided again while behavioral performance remained stable. A very similar pattern was found when investigating post-synaptic dendritic spines (Xu *et al.*, 2009). Mice trained in a reaching task experienced a rapid formation of new dendritic spines within an hour. This rapid increase was then followed by a slower process of elimination of "old" spines that had existed before training, returning the overall number of spines to a comparable pre-training level, despite continuously high performance levels (Xu *et al.*, 2009). Taken together, these results from animal literature and the few reports in humans of structural alterations even after very short periods of time call for a closer investigation of the temporal dynamics of gray matter changes.

Actually already in 1894, Santiago Ramón y Cajal – by many thought to be the father of modern neuroscience – proposed that mental activity might induce „*novel intercellular connections through the new formation of collaterals and protoplasmic expansions*". He then raised the intriguing question: *"How can the volume of brain remain constant if there is a multiplication and even new formation of terminal branches of protoplasmic appendices and nerve collaterals?"* (Azmitia, 2007). More than 100 years and numerous studies demonstrating experience-dependent growth of human brain volume later, we are confronted with the same paradox: Is it really feasible to represent the vast amount of knowledge and skills that humans acquire during a whole lifetime as a process of continuous brain volume growth? Importantly, prominent theoretical accounts of plasticity, developmental data, and animal models as described above provide a different account of plasticity, according to which plasticity follows a sequence of expansion, selection, and renormalization.

Informed by this notion, we acquired up to 18 structural MR images over a 7-week period while right-handed adult participants practiced left-hand writing and drawing (Wenger, Kühn, *et al.*, 2017). We observed that gray matter in primary motor cortices expanded during the first weeks of motor learning and then partially renormalized, in the presence of continued practice and increasing task proficiency. We therefore propose that plastic reorganization processes in the context of skill acquisition consist of an initial but transient phase of brain volume increase followed by partial or even complete return to baseline once optimal rewiring has occurred (Wenger, Brozzoli, *et al.*, 2017). Importantly, this pattern of plastic change seems to hold true across different levels of plasticity, so far mostly investigated in animal models: Cortical map plasticity follows a comparable pattern of expansion followed by renormalization during learning (Peters, Chen and Komiyama, 2014; Albieri *et al.*, 2015; Pruitt *et al.*, 2016). Also work on learning-related changes in dendritic spines is consistent with the hypothesis that the memory trace serving skilled performance is localized in rewired circuitry rather than in any large-scale expansion (Holtmaat and Svoboda, 2009; Hofer and Bonhoeffer, 2010; Fu and Zuo, 2011). Motor sequence learning has been shown to be associated with increasing motor system activity in the early stages of learning, followed by a reduced level of motor system activity during execution of highly practiced motor behavior (Wymbs and Grafton, 2015). Metabolic efficiency might be a driving factor behind this pattern (Makino *et al.*, 2016), as learnt information can be represented by a relatively smaller number of spikes or neurons after learning compared to before (Makino and Komiyama, 2015; Chu, Li and Komiyama, 2016). While during initial stages of learning, more neurons and synapses are being used, thereby potentially entailing an expansion of tissue in these regions due to metabolic demands, later on, the most efficient wiring is selected, resulting in fewer but specialized and stable neurons and synapses (Makino *et al.*, 2016).

This pattern of experience-dependent initial production of diversity followed by selection and stabilization has the features typically ascribed to Darwinian models of cortical

plasticity and neural development (Fernando, Szathmáry and Husbands, 2012; Kilgard, 2012). Within this framework, plastic changes may be seen like an audition for the cast of a movie. Numerous candidates are first progressively called in, then the best ones are selected and the rest is sent home, that is, "pruned away". Calling in more candidates may possibly improve the outcome; growth can therefore be helpful, but is not the end product.

An expansion-renormalization model of experience-dependent structural brain changes predicts initial learning-dependent volumetric increase of brain structure – reflecting recruitment of additional neural resources and local neural rewiring – followed by a partial or complete return to baseline once optimal rewiring has occurred and the surplus has been eliminated. This way, space restriction within the skull and therefore competition between different brain regions and skills are not an issue. The expansion-renormalization model thus gives motivation for a new look at past findings on experience-dependent plasticity in humans and raises several new research questions and predictions for work on human experience-dependent plasticity probed with MRI (Lindenberger, Wenger and Lövdén, 2017; Wenger, Brozzoli, *et al.*, 2017) .

Conclusion

In the last years, evidence has accumulated suggesting that brain structure can change in response to altered environmental demands. Such structural changes have been observed in rodents after enriched housing, and also in humans for example following intensive studying, musical experience, video game playing or spatial navigation or the training of a new skill such as juggling, and has also been observed throughout the lifespan.

Much of this research used MRI, which allows for in-vivo investigations of human brain structure with increasingly informative acquisition sequences. A future challenge is and remains to determine the cellular and molecular changes that underlie the macrostructural changes visible on MR images (see also Colzato and Hommel this volume). Meeting this

challenge requires greater exchange between those studying human populations and those working with animal models, and a greater integration of techniques. Animal studies in which both imaging and histological measures can be applied in parallel will be particularly helpful to establish the relative contributions of different cellular processes to the MRI effects. At the same time, one will need to keep in mind that multiple, coordinated cellular processes are most likely associated with changes in a single MR-based variable and that phenomena detected in rodents might not generalize fully to humans or vice versa.

Endless expansion may not be nature's best solution to the phenomenon of lifelong learning when in other parts of evolution processes of trimming and selecting the best among several candidates has proven immensely useful. We have therefore proposed that plastic changes (specifically in the context of skill acquisition) are characterized by a sequence of volume expansion, selection, and renormalization. More complex study designs with at least three or more measurement time points are necessary to make appropriate use of the aforementioned sophisticated hardware and software tools and to eventually gain more knowledge on the phenomenon of brain plasticity, its temporal dynamics, functional relevance, and biological mechanisms.

At a more general level, we hope to have succeeded in affirming the complexity of neuroplasticity. This should not come as a surprise since Pascual-Leone and colleagues (2005) have already asserted that neuroplasticity constitutes evolution's invention to enable the nervous system to escape the restrictions of its own genome and adapt to environmental demands. Understandably enough, this should indeed constitute a complex and dynamic process that is hard to gauge and that remains highly interesting to study in the future in even more detail.

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