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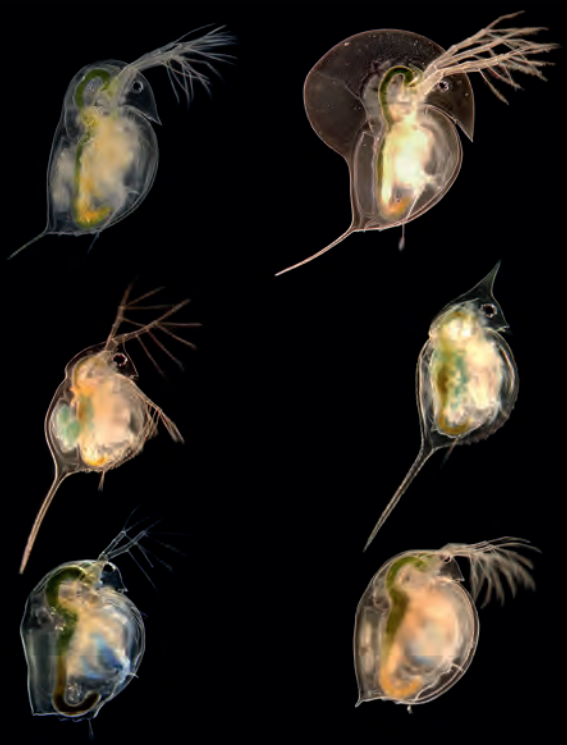

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COVER ILLUSTRATION A prime example of phenotypic plasticity are inducible defenses initiated through chemical signalling cues in the freshwater crustacean Daphnia. Different predator odours induce defensive strategies in the different Daphnia species. a. undefended D. longicephala, which when exposed to b.) the predator the heteropteran backswimmer Notonecta glauca c.) expresses extensive crests. d.) undefended D. lumholtzi which when exposed to e.) three-spined sticklebacks (Gasterosteus aculeatus) f.) express elongated head and tail spines. g.) undefended D. magna that when exposed to h.) the tadpole shrimp Triops spec. expresses i.) bulkier bodies. Photos by Joshua Huster, not to scale. Cover illustration provided by Linda C. Weiss, Neurobiology of phenotypic plasticity in the light of climate change, (nf-2021-0029, pp. 1–12 in this issue).

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Review article

Linda C. Weiss*

Neurobiology of phenotypic plasticity in the light of climate change

https://doi.org/10.1515/nf-2021-0029

Abstract: Phenotypic plasticity describes the ability of an organism with a given genotype to respond to changing environmental conditions through the adaptation of the phenotype. Phenotypic plasticity is a widespread means of adaptation, allowing organisms to optimize fitness levels in changing environments. A core prerequisite for adaptive predictive plasticity is the existence of reliable cues, i.e. accurate environmental information about future selection on the expressed plastic phenotype. Furthermore, organisms need the capacity to detect and interpret such cues, relying on specific sensory signalling and neuronal cascades. Subsequent neurohormonal changes lead to the transformation of phenotype A into phenotype B. Each of these activities is critical for survival. Consequently, anything that could impair an animal's ability to perceive important chemical information could have significant ecological ramifications. Climate change and other human stressors can act on individual or all of the components of this signalling cascade. In consequence, organisms could lose their adaptive potential, or in the worst case, even become maladapted. Therefore, it is key to understand the sensory systems, the neurobiology and the physiological adaptations that mediate organisms' interactions with their environment. It is, thus, pivotal to predict the ecosystem-wide effects of global human forcing. This review summarizes current insights on how climate change affects phenotypic plasticity, focussing on how associated stressors change the signalling agents, the sensory systems, receptor responses and neuronal signalling cascades, thereby, impairing phenotypic adaptations.

Keywords: chemoreception; nervous system; ocean and freshwater acidification; pCO_2; temperature.

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Zusammenfassung: Die phänotypische Plastizität beschreibt die Fähigkeit eines Organismus mit einem bestimmten Genotyp, auf veränderte Umweltbedingungen durch die Anpassung des Phänotyps zu reagieren. Die phänotypische Plastizität ist ein weit verbreitetes Mittel der Anpassung, das es Organismen ermöglicht, ihre Fitness in einer sich verändernden Umwelt zu optimieren. Eine wesentliche Voraussetzung für die adaptive prädiktive Plastizität ist das Vorhandensein zuverlässiger Hinweise, d. h. genauer Umweltinformationen über die künftige Selektion auf den ausgeprägten plastischen Phänotyp. Darüber hinaus müssen Organismen in der Lage sein, solche Hinweise zu erkennen und zu interpretieren, wobei sie sich auf spezielle sensorische Signalwege und neuronale Kaskaden stützen. Die anschließenden neurohormonellen Veränderungen führen zur Umwandlung von Phänotyp A in Phänotyp B. Jede dieser Aktivitäten ist für das Überleben entscheidend. Folglich könnte alles was die Fähigkeit eines Tieres wichtige chemische Informationen wahrzunehmen beeinträchtigen könnte, erhebliche ökologische Auswirkungen haben. Der Klimawandel und andere menschliche Stressfaktoren können auf einzelne oder alle Komponenten dieser Signalkaskade einwirken. In der Folge könnten Organismen ihr Anpassungspotenzial verlieren oder können im schlimmsten Fall sogar Fehlanpassungen entwickeln. Daher ist es von entscheidender Bedeutung, die sensorischen Systeme, die Neurobiologie und die physiologischen Anpassungen zu verstehen, die die Interaktionen von Organismen mit ihrer Umwelt vermitteln. Es ist daher von zentraler Bedeutung, die Auswirkungen globaler menschlicher Einflüsse auf das gesamte Ökosystem vorherzusagen. Dieser Übersichtsartikel fasst die aktuellen Erkenntnisse darüber zusammen, wie sich der Klimawandel auf die phänotypische Plastizität auswirkt, wobei der Schwerpunkt darauf liegt, wie die damit verbundenen Stressoren die Signalstoffe, die sensorischen Systeme, die Rezeptorantworten und die neuronalen Signalkaskaden verändern und dadurch die phänotypischen Anpassungen beeinträchtigen.

Schlüsselwörter: Chemorezeption; Nervensystem; Ozean- und Süßwasserversauerung; pCO_2; Temperatur.

Introduction

Phenotypic plasticity

Ecological communities are assemblages of populations with interacting species. Species interact within each other, between each other and with their spatially and temporally dynamic environment. In order to cope with such ever-changing conditions, organisms need the capacity to detect and decipher the relevant stimuli from their surrounding and then react appropriately (DeWitt and Scheiner, 2004; Kirkpatrick and Price, 2008). Phenotypic plasticity is a widespread mean that allows organisms with a given genotype to respond to changing conditions by adaption of the phenotype (Bradshaw, 1965, Figure 1). Phenotypic responses can involve far-reaching changes in morphology, biochemistry, physiology, metabolism, behaviour, life history parameters and even the combination of all of these. Taken together, these changes result in the development of an environmentally adapted phenotype (Figure 2 displays different examples of phenotypic plasticity). This phenotype is then, literally spoken, the sum of all traits; i.e. when expressing behavioural changes, this often requires the development of certain morphological features, in line with the necessary hormonal conditions that regulate movements and coordinate the performance of complex behaviours that finally improve organismal fitness in the new environment (West-Eberhard, 2008). As phenotypic plasticity shapes ecological patterns and processes, it thereby contributes to the diversity, stability and persistence of communities, populations and species (Miner et al., 2012; Verschoor et al., 2004). It is even speculated to pave way for speciation (Pfennig et al., 2010; West-Eberhard, 2005).

At the forefront of this whole reaction in many cases stands the nervous system, as it lays the fundamental basis to detect and interpret abiotic and biotic environmental conditions (Figure 1).

Upon this, the current state of a pre-existing phenotype is caused to change. Potential factors that trigger phenotypic changes are manifold and can act individually or in combination. For example, inducing agents may be abiotic changes in light regime (e.g. photoperiod length; see Excursion 1). Or the inducing agent can result from biotic changes in the chemical environment where chemical signalling cues (also referred to as semiochemicals (Figure 3), which are chemicals or chemical mixtures that affect the phenotype of another organism) engage in interspecific and intraspecific information transfer.

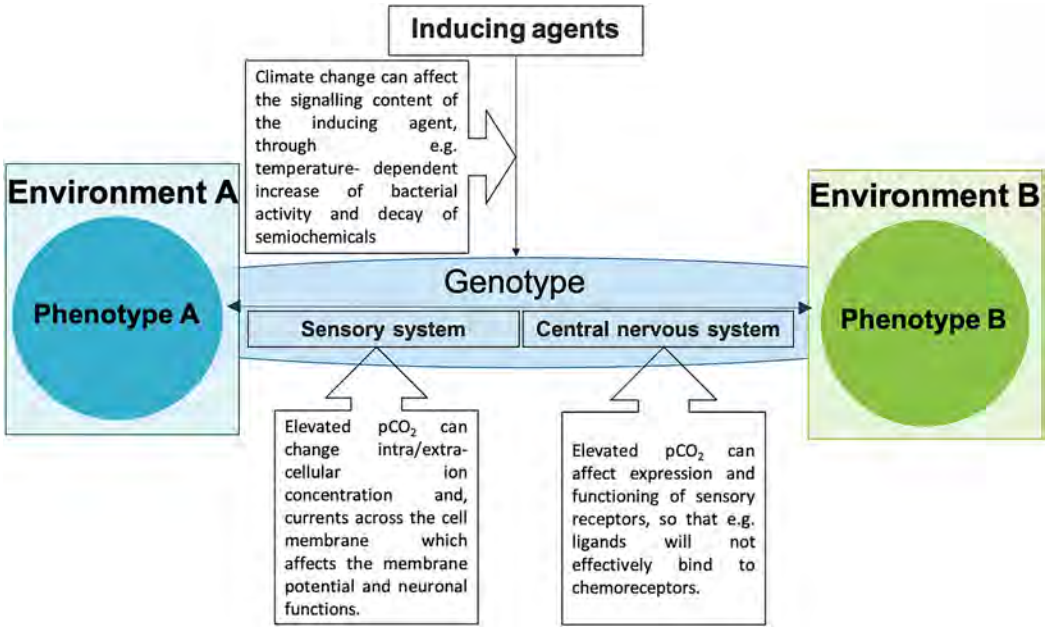

Figure 1: Phenotypic plasticity comprises a sequence of biological reactions that is initiated upon the perception of an inducing agent. This inducing agent can be of abiotic or biotic nature including changes in photoperiod or temperature regime, light conditions, and chemical signalling agents released by conspecifics and/or heterospecifics. Organisms can sense these changes in the environment through specific sensory systems. The change in the environment then has to be interpreted by the central nervous system. Through (neuro)-endocrine pathways effector systems (e.g. specific cellular targets that start to proliferate), phenotype A is transformed into phenotype B. By this, organism fitness is optimized to the new environmental condition. Climate change can affect different steps in this sequence leading to maladaptation, thereby reducing organism fitness. Or, climate change could affect all or individual components in this sequence, thereby impairing the organisms' ability to react plastically.

A multitude of anthropogenic stressors can have a direct impact on the nervous system, thereby hindering organism and environmental interactions (see Excursion 2).

In other cases, climate change acts through different paths and hampers environmental perception through (1) modifying the signalling agent or (2) deteriorating sensory/neuronal capacities. For example, a chemical signalling agent may decay due to temperature-dependent increase of bacterial activity or inducing agents being misinterpreted, e.g. through direct or indirect deficits of the sensory nervous system. This can prevent the correct interpretation of the environment and lead to inappropriate responses (Chivers et al., 2014; Weiss and Tollrian, 2018). This review focuses on those anthropogenic stressors that stem from climate changes, i.e. (1) elevated temperature and (2) in aquatic systems, an elevated level of CO_2 partial pressure (pCO_2) that is accompanied with a reduction in water pH. Special emphasis will be laid on chemoreception in aquatic systems (but see Excursion 3). Here, many studies have shown as to how increasing temperature and decreasing pH affect the nervous system and thereby hamper chemical information transfer within species. This ultimately affects behavioural or other phenotypic patterns.

Chemoreception: detecting friends and foes using chemical signalling cues

Semiochemicals are signalling chemicals that inform about the presence and absence of mating partners and help to locate food sources, and some organisms even use distinct chemical cues to locate optimal breeding grounds (Pohnert et al., 2007; Wisenden, 2000). Other semiochemicals inform about the presence and activity level of predators which stimulate the expression of defensive strategies (Weiss and Tollrian, 2018; Weiss et al., 2012). These defences can be shown in forms of alternative behavioural patterns, like seeking refuge, or the expression of morphological defence structures imposing handling difficulties on predators (Figure 3).

In the sender and receiver context, semiochemials that transfer information within the same species and induce plasticity by initiating a certain behaviour are referred to as pheromones. For example, pheromones in forms of urinary odorants are widely used in sexual chemical communication, such as fishes, crustaceans and rodents (Gomez-Diaz and Benton, 2013). Other cues that act interspecifically are alarm cues. These chemicals are released from injured conspecifics

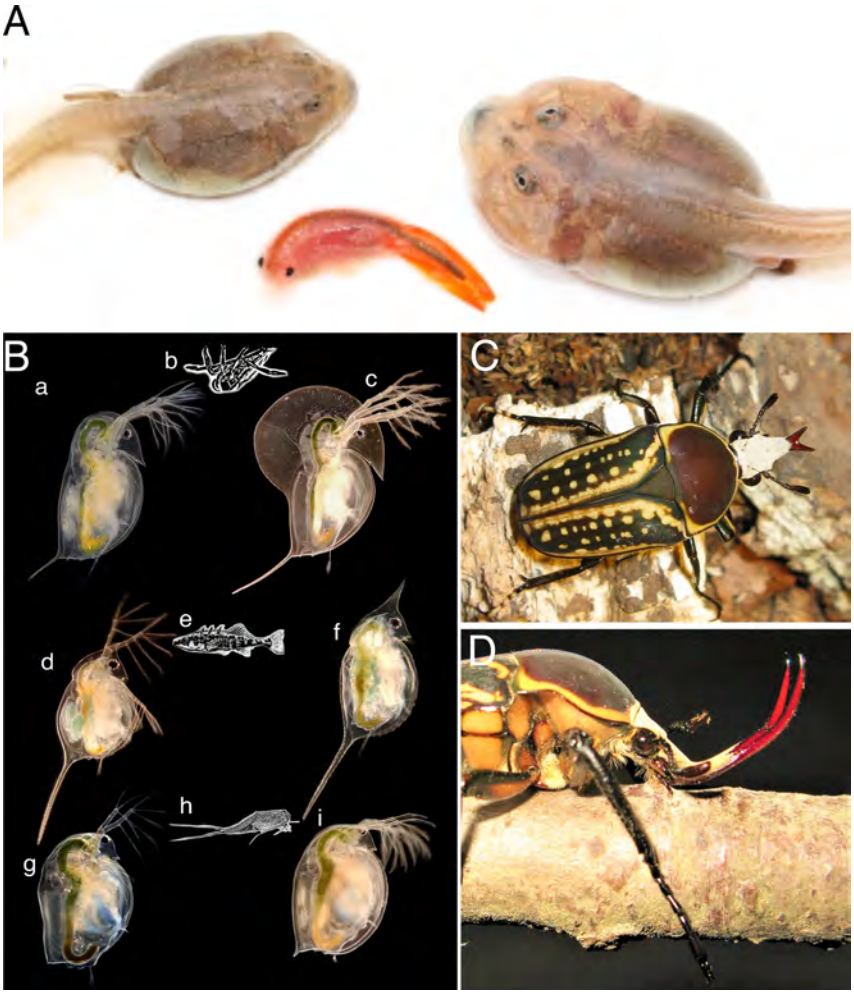

Figure 2: Examples of phenotypic plasticity.
(A) Phenotypic plasticity in Mexican spadefoot toad tadpoles (*Spea multiplicata*), which develop into either an omnivore morph (left) or carnivore morph (right), which is induced by, and specializes on, fairy shrimp (center). Photos by David Pfennig. **(B)** A prime example of phenotypic plasticity are inducible defenses initiated through chemical signalling cues in the freshwater crustacean *Daphnia*. Different predator odours induce defensive strategies in different *Daphnia* species. (a) Undefended *Daphnia longicephala*, which when exposed to (b) the predator, the heteropteran backswimmer *Notonecta glauca* (c) expresses extensive crests. (d) Undefended *Daphnia Lumholtzi*, which when exposed to (e) three-spined sticklebacks (*Gasterosteus aculeatus*) (f) express elongated head and tail spines. (g) Undefended *Daphnia magna* that when exposed to (h) the tadpole shrimp *Triops* spec. expresses (i) bulkier bodies. Photos by Joshua Huster, not to scale.
(C) *Mecynorhinaharrisiieximia* (AURIVILLIUS1886) horn beetle male without exaggerated secondary sexual structure and **(D)** with pronounced sexual secondary structure. Males use their horns to fight over females, but horns are not developed when exposed to limited resources. Photos by André Mursch.

and invoke adaptive responses to reduce the predation risk (Ferrari et al., 2010). Allelochemicals act within individuals of different species. A special type, i.e. kairomones, transfer information with a beneficial effect for the sender only. Kairomones are especially known for mediating predator and prey interactions. Predator species unintentionally release kairomones that induce morphological and/or behavioural defences in the prey. These inducible defences are a prime example of phenotypic plasticity (Pohnert et al., 2007; Weiss et al., 2018a). Each of these semiochemical-induced changes is critical for survival (Pohnert et al., 2007; Wisenden, 2015). Unfortunately, only a handful of all these signalling agents have been chemically identified. In addition, the origin of semiochemicals is often unknown; therefore, it is undetermined from where and/or under what circumstance they are released.

Without knowing the chemical composition of semiochemicals, estimates on the impact of climate change and chemical pollutants are difficult to foresee. The ways in which these chemicals are affected by temperature, changes in surrounding pH, or elevated levels of pCO_2 are vague. Possible modifications rely on the chemical nature of the cue,

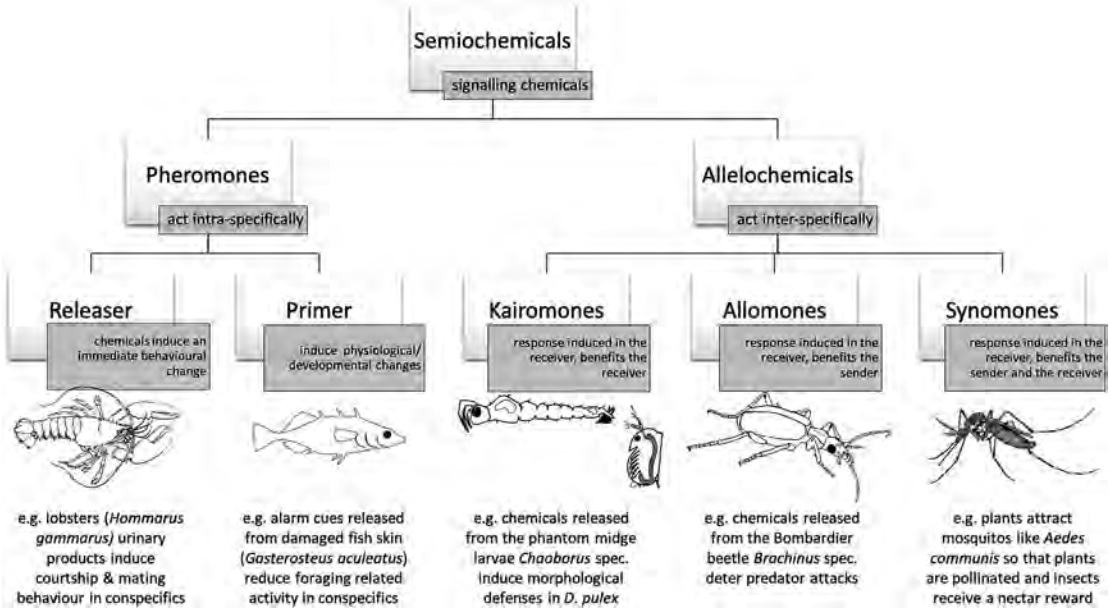

Figure 3: Schematic display of the sub-categories of semiochemicals with specific examples.

e.g. peptides may suffer from protonation in the context of ocean acidification (Draper and Weissburg, 2019; Lecchini et al., 2017; Roggatz et al., 2016). Further modifications could occur if stressors augment the production of the chemical cue, i.e. when the cue is associated with metabolic pathways, an increased temperature-dependent metabolic activity could lead to an overproduction of the agent. This would stimulate a stronger phenotypic response in the receiver than necessary. This is problematic when considering that such adaptations often evolve in a cost-benefit optimised framework, so that the costs that are associated with the expression of such adaptive features outweigh the benefits. A reduced production would have the opposite effect, and the prey may not be defended and thereby become more prone to predation. In fact, CO_2 was found to directly reduce the production of alarm cues in aphids (Boullis et al., 2017; Draper and Weissburg, 2019). In another instance, high temperature levels have been seen to accelerate pheromone decay as a result of increased bacterial degradation activity (e.g. trail-following behaviour is compromised through bacterial pheromone decay in the ant species *Tapinoma nigerrimum*; Groot and Zizzari, 2019; van Oudenhove et al., 2011). Likewise, alarm cues are released when the skin of fish (such as the blacknose shiner, *Notropis heterolepis*) is damaged (e.g. during a predatory attack), this elicits an unlearned predator avoidance response in conspecifics (Wisenden et al. 2004).

However, information transfer is affected not only by semiochemical concentration changes, but also by stressors that can cause chemical modifications to semiochemicals. These changes hamper perception in the receiving organisms. Under acidic conditions (pH~6), fathead minnows (*Pimphales promelas*), finescale dace (*Phoxinus neogaeus*), pumpkinseed fish (*Lepomis gibbosus*), rainbow trout (*Oncorhynchus mykiss*) and brook charr (*Salvelinus fontinalis*) display a reduced ability to respond to these alarm cues. The pre-exposure of just the alarm cue to weakly acidic conditions diminished the behavioural effect such that not olfaction is affected but the chemical cue itself (Draper and Weissburg, 2019; Kelley et al., 2018).

It would be important to see how severe these effects can potentially be and modify different semiochemicals. Likewise, an important question would be about how this changes chemical perception. In fact, chemoreceptors, in general, are widely tuned (Baker et al., 2004), which means that they do not bind to just one ligand but several similarly composed ligands. Smaller chemical modifications of semiochemicals could be unnoticed and thus not change chemical interactions. By contrast, pheromone detection, which, e.g. in *Bombyx mori*, is a prime example of a chemoreceptor that is specifically tuned and only responds to one chemical, i.e. the bombykol (Baker et al., 2004), is not well-studied in aquatic species. If such a highly specific semiochemical × receptor interaction is hampered through climate change and polluting stressors, this could largely affect species reproduction with potential demographic consequences. It is, thus, relevant to better understand chemoreception *per se*, and how the environment can change the chemoreceptive processes.

Chemoreceptor sensitivity and functioning

Temperature effects

The first step of chemoreception is the interaction between a semiochemical and membrane-bound receptors. Climate change could alter the chemoreceptor tuning to its ligands and thereby affect this step within information transfer. For example, temperature was shown to alter the olfactory sensitivity in *Drosophila melanogaster* which results from odour concentration changes in the gas phase due to temperature-dependent volatility changes. The olfactory system can adapt to these changes and already acclimate on the receptor level. Within normal temperature ranges (15–30 °C), the olfactory system adapts to such fluctuations so that the olfactory system provides accurate information to the animal. Changes in olfactory responses begin during the reception process at the neuron receptor level. The associated response pattern is independent of the duration (hours vs days) of the temperature incline. On the molecular level, differences in gene expression patterns were found showing that, upon others, the expression level of chemoreceptor genes changes in a temperature-dependent manner (Riveron et al., 2013). Under future temperature levels, it is uncertain whether such adaptive capacities remain or if temperature fluctuations become too strong and too long-lasting and affect animal olfaction (Riveron et al., 2013). Moreover, a lot less is known for aquatic species where especially chemosensory mechanisms are not well-studied, and there is only limited information on the involved chemoreceptors and their environment-dependent expression patterns, three-dimensional structure and co-expression with possible co-receptors. This makes it difficult to estimate not only temperature effects but also effects that result from increased levels of pCO_2, which are accompanied by pH declines.

Effects of elevated pCO_2 and decreased pH

While temperature inclines seem to be a global problem affecting terrestrial and aquatic ecosystems, elevated levels of pCO_2 are known to react with sea and freshwater,

thereby affecting water chemistry (Doney et al., 2009; Hasler et al., 2016; Phillips et al. 2015; Weiss et al., 2018b). The pCO_2-dependent aquatic acidification was shown to impair the adaptive potential of different vertebrate and invertebrate species in fresh and salt water (Doney et al., 2009; Hasler et al., 2016; Phillips et al., 2015; Weiss et al., 2018b). In fact, not only species with carbonate shells or skeletons are disturbed in their growth rates and overall fitness levels, but also olfactory abilities are hampered through which animals (especially fish) become disoriented (Ellis et al., 2017). In particular, fish exposed to elevated CO_2 levels showed corresponding reductions in the electro-olfactogram recorded at the olfactory epithelium, suggesting that CO_2 acts to impair olfactory sensitivity (Ou et al. 2015). This has the potential to result in changes of behavioural responses showing significant alterations in olfactory abilities with maladaptive anti-predator strategies and increased anxiety (Ou et al., 2015). Even field experiments have shown that under these high pCO_2 conditions, juvenile Atlantic salmon experience greater predation rates (Elvidge et al., 2014). To understand how pCO_2-dependent aquatic acidification affects chemoreceptor functioning, it is first important to delineate what hinders receptor-ligand interactions, i.e. is it the increased level of free CO_2 in the aquatic medium, or is it the resulting reduction in environmental pH? pH is a critical factor for any kind of protein activity and also for receptor functioning (Traynelis et al., 2010). Likewise, elevated levels of pCO_2 could modify organism behaviour. Many invertebrate species have CO_2 receptors with the potential to impinge on many complex behaviors ranging from foraging to oviposition to predator avoidance responses (Stange and Stowe, 1999). However, elevated pCO_2 and temperature inclines not only affect the sensory structures and pathways, but both stressors can have central effects.

Central nervous system and neuronal signalling pathways

Central effects of temperature inclines

Temperature directly affects biochemical reactions, thereby influencing the rate of biological processes from the cellular to the organismal level (Kelley et al., 2018; Kingsolver, 2009). Not only does temperature affect organism metabolism, it also changes nervous system development by which changes of neuronal attributes can expand from the receptor to the system level. Further, the thermal environment can influence neurogenesis in adult brains (Feng, 2014; O'Donnell, 2018). These developmental changes in neural systems are likely to impact behaviour (e.g. feeding and migration) and are compounding in combination with other impacts such as heat-related stress and mortality (O'Donnell 2018). In humans, an increase in temperature leads to a significant increase in migraine, as reported by German population (Ruszkiewicz et al., 2019).

In vertebrates, one regulator of thermal plasticity is the hypothalamic-pituitary-adrenal/interrenal (HPA) axis. This axis serves as an important physiological regulator of temperature changes through the actions of two glucocorticoid hormones, cortisol and corticosterone (Jessop et al., 2018).

Both can have broad-scale effects and change gene transcription that allow for diverse and complex control of adaptive physiological features including metabolism, reproduction, growth and immune functions, and this axis is, therefore, a prime target to study the effects of climate-change-dependent temperature inclines (Jessop et al., 2018).

Direct-temperature-dependent effects may be transmitted by the transient receptor potential channel protein (TRP) gene family. TRP receptors are phylogenetically highly conserved and expressed in many different types of cells, including sensory cells. These could, therefore, be of special interest for studying climate-change-associated temperature sensation and associated changes in a range of taxa (Hutson et al., 2017). For example, the heat activation of the TRPV4 and the TRPV1 channel is responsible for birth defects in chick and zebrafish embryos (Hutson et al., 2017). Already there is evidence that climate-change-associated thermoconstancy affects human fetal development and health (Kalisch-Smith et al., 2020; Lin et al., 2019). Here, congenital heart defects could be explained by hyperthermia that activates ion channels and change foetal development (Hutson et al., 2017). Through similar mechanims, gene expression patterns could become engaged in neurons, leading to an alternate neuron structure and finally affecting global brain organization (O'Donnell, 2018). Not only climate-change-dependent temperature increases but also elevated levels of pCO_2 causing declining pH of ocean water are discussed to affect neuronal functioning.

Central effects of elevated pCO_2

Invertebrate and vertebrate taxa have been found to be susceptible to elevated pCO_2 in aquatic environments. When organisms experience such significant environmental challenges in pH and pCO_2, this is followed by changes in the intracellular chemistry. Many of the phenotypic effects included an increase in the overall activity and a misinterpretation of chemical cues elicited by conspecifics and heterospecifics. In consequence, organisms must alter their energy budget to accommodate the physiologically associated expenditures often affecting growth and reproduction (Thor and Dupont, 2015).

Specifically, fish species have been intensely investigated with respect to their susceptibility under elevated levels of pCO_2 and decreasing pH (Lecchini et al., 2017; Munday et al., 2012; Tresguerres et al., 2020). A wealth of papers from the past decade had shown that pCO_2 leads to sensory impairments, changes neuronal signalling and disables learning capabilities (Draper and Weissburg, 2019). These changes were suspected to be rooted in a specific mechanism involving inhibitory neuronal signalling (Tresguerres and Hamilton, 2017). Due to the chemical reaction of atmospheric CO_2 with ocean water, carbonate equilibria are modified and pH is reduced, upon which intra- and extracellular levels of carbonate and chloride ion gradients are shifted, affecting the function of the neurotransmitter gamma-aminobutyric acid (GABA), rendering inhibitory actions excitatory (Nilsson et al., 2012). This so-called $GABA_A$ receptor ($GABA_AR$) hypothesis was then mounted on the fact that the application of the $GABA_A$ receptor antagonist gabazine diminished ocean-acidification-dependent effects. However, Tresguerres and Hamilton (2017), nicely pointed out some yet unresolved questions that need to be clarified before supporting or disproving the $GABA_A$ hypothesis. They discussed that the actual [HCO_3^-], [Cl^-] and pH levels in the relevant intra- and extracellular fluids are not known and therefore, it is uncertain to assume if relevant pCO_2 levels can actually cause these significant alterations of parameters. Likewise, the membrane potential of neurons from many marine organisms seems undetermined similar to the $GABA_AR$ permeabilities for Cl^- and HCO_3 (Tresguerres and Hamilton, 2017). Further, Tresguerres and Hamilton (2017), discussed that neuronal mechanisms other than $GABA_AR$-mediated responses could be affected by pCO_2, including the permeability of glycine receptors, the overall neuronal network dynamics, astrocyte–neuron metabolism and CO_2-sensing peripheral neurons, to name a few (Tresguerres and Hamilton, 2017). In addition, hypercapnia (which is the elevation of pCO_2in blood or hemolymph) in general has a narcotic effect on fish and invertebrates (Marking and Meyer, 1985), and maybe there is a yet-undetermined direct action of pCO_2 on neurotransmitter–receptor functioning or alike.

Now, there is mounting evidence that the effects previously reported were overestimated, and that elevated levels of ocean pCO_2 on fish behaviour are probably less drastic (Clements et al., 2020) but not absent under specific conditions (Munday et al., 2020). As marine fish have well-developed acid–base regulatory systems to maintain tissue pH, it does not seem surprising that when faced with pCO_2 levels that exceed 15,000 µatm (current marine pCO_2 level is at ~400 µatm) (Clark et al., 2020), they are able to adjust to such environmental changes. However, the question is about how long they can accommodate to such persistent environmental changes. In addition, these experimentally applied levels are just the for 2100 prognosed average levels of pCO_2 (i.e. ~1000 µatm). However, in coastal regions, pCO_2 fluctuates due to biological reef metabolism associated with organic matter decomposition, and peak periods may intensify in

magnitude and frequency to exceed physiological levels. Such fluctuations could stress an organism's physiology, but this is not in the focus of recent scientific engagements (Ishida et al., 2021; Matthew and Danielle, 2021). Further, a lot less is known about the nervous system responses of invertebrate species that are also affected by increased levels of pCO_2. For example, in freshwater, the microcrustacean *Daphnia* becomes more prone to predation, as pCO_2 affects its sensory capacities rendering it less defended against its predator, the phantom midge larvae *Chaoborus* spec. (Weiss et al., 2018b). In this experiment, it was also tested whether the sensory deficits are rooted in the decrease in pH or the increase in pCO_2. In fact, pH is a significant factor for receptor functioning. Many neurotransmitter–receptors function only in a strictly pH-dependent manner so that protons inhibit all glutamate receptors and could thereby change synaptic plasticity, glutamate release and glutamate uptake to cause neuropathological conditions including stroke and seizure (Traynelis et al., 2010). Further, protons can have neurotransmitter functions themselves and activate acid-sensing ion channels, regulating synaptic plasticity. It is therefore of utmost importance to delineate the cause of aquatic-acidification-dependent changes in sensory sensitivities.

In *Daphnia*, elevated pCO_2 caused the sensory deficits through yet undetermined mechanisms. Similar observations were made in *Daphnia's* predator, *Chaoborus*. Under elevated pCO_2, these predatory larvae do not strike as efficiently for their prey (Kowalewska et al., 2020). At the same time, *Chaoborus* larvae perform more undirected movements through which energy requirements further increase. Then, these might not be met, when not being effective in prey capture (Kowalewska et al., 2020). The underlying neuronal mechanisms are, however, still completely elusive.

To improve the overall understanding of how different taxa are affected by elevated levels of pCO_2 accompanied by pH declines, it is of utmost importance to understand how these stressors affect the nervous system in these taxa and during different life stages. This further requires the use of strategies through which intracellular ion currents for different receptor types could be determined *in vitro* and in extracellular recordings measuring spike rates *in vivo* to obtain insights into the systemic response.

Conclusions

It is understood how organisms perceive their environment determines their life. If these abilities are augmented by environmental stressors, this can have far-reaching consequences. We need to understand, now more than ever, how animals and plants respond to natural and anthropogenic variation in the environment in order to predict, prevent and/or mitigate negative impacts on our biospheres. In this regard, it is pivotal to study the sensory capacities also in non-model species using strategies that will reveal climate-change-dependent impairments from the receptor level up to the systemic responses.

It will further be important to understand that climate change is not just one pervasive stressor, but it encompasses the interplay of several stressors that are not static but fluctuate, which becomes even more complicated when combined with naturally occurring stressors (e.g. predators). It will be intriguing to see the overlap and contrasts in molecular mechanisms that beget adult seasonal/hierarchical phenotypic plasticity in different taxa. Long-term acclimation and trans-generational studies need to reveal mechanistic information on physiological processes potentially affected by anthropogenic stressors and will allow us to identify species- and life-stage-specific differences that could point out 'winners and losers'. There will be instances under which phenotypic plasticity will enable the organisms to adapt to anthropogenic stressors; also, there will be instances where stressors will impair the organism ability to react plastically, and this will most likely transfer to the ecosystem level and change community structures and biodiversity.

Excursion 1: Phenotypic mismatches to environmental conditions

Light is one important factor that tunes the rhythmicity of specific behaviours (e.g. reproduction, migration, (in) activity) to diel, lunar, and seasonal cycles. With opsin and cryptochrome receptors located on special nerve cells, organisms can sense changes in the light (spectral/intensity) and photoperiodic regimes (daily, annual) controlling their chronobiology (Häfker and Tessmar-Raible, 2020). Urbanization-associated light pollution can disrupt this temporal niche use so that organisms are less well-adapted to their environment with consequences for their fitness. For example, the magnitude of circadian clock-controlled diel vertical migration in the freshwater crustacean *Daphnia* is reduced by nocturnal light (Häfker and Tessmar-Raible, 2020; Moore et al., 2000; Rund et al., 2016). Furthermore, seasonal coat-colour changes in mammals and birds of polar regions are controlled by physiological mechanisms entrained by photoperiod and optimized to match local conditions (Zimova et al., 2018).

However, as seasonal duration and extent of snow cover decline through increasing global temperatures, species become colour-mismatched to their environment. In consequence, they lose the advantageous effect of seasonally tuned camouflage (Zimova et al., 2018).

Excursion 2: Pollutants disrupting sensory abilities

It is important to mention that there are also anthropogenic pollutants that can disrupt sensory systems, even at low, non-toxic concentrations (Troyer and Turner, 2015). Heavy metals are known to have toxicological effects on the mechanosensory lateral line system of fish. Being externally located, they are directly exposed to compounds in the surrounding environment and therefore prone to damage. In zebrafish (*Danio rerio*), for example, the level of damage to the neuromasts depends on the concentration of dissolved copper. Doses above 50 µg/L lead to an almost complete cell death (Kelley et al., 2018; McNeil et al., 2014). Subsequent studies with larval zebra fish have shown that exposure to both copper ($CuSO_4$) and silver ($AgNO_3$) metal salts is associated with a reduction in the number of neuromasts and a failure to orientate in a water current (Kelley et al., 2018; McNeil et al., 2014). Further stressors described include chemicals belonging to the group of antidepressants that enter aquatic systems through waste waters. These pharmaceuticals are designed to interfere with neuronal signalling cascades and thus have a foreseeable but often not described effects on species' (neuro)-physiology, populations and community structures.

Excursion 3: Further examples of sensory systems prone to climate change

Elevated pCO_2 effects have been tested on the capacity of visual detection in larval temperate gobies (*Gobiusculus flavescens*). The animals show an increase in phototactic activity, suggesting a visual hypersensitivity (Forsgren et al., 2013). Further, the flicker fusion threshold, a capacity important for movement tracking, was found to be reduced in spiny damselfish (*Acanthochromis polyacanthus*) (Chung et al., 2014). Elevated pCO_2 can also directly change auditory sensitivity through an increased otolith size used by fish to detect sound waves (Bignami et al., 2013; Shen et al., 2016). Such a hypersensitivity may impair the ability to discriminate behaviourally relevant auditory cues from 'background noise'.

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Bionote

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Review article

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What the eye tells the brain: retinal feature extraction

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Abstract: To provide a compact and efficient input to the brain, sensory systems separate the incoming information into parallel feature channels. In the visual system, parallel processing starts in the retina. Here, the image is decomposed into multiple retinal output channels, each selective for a specific set of visual features like motion, contrast, or edges. In this article, we will summarize recent findings on the functional organization of the retinal output, the neural mechanisms underlying its diversity, and how single visual features, like color, are extracted by the retinal network. Unraveling how the retina – as the first stage of the visual system – filters the visual input is an important step toward understanding how visual information processing guides behavior.

Keywords: color vision; retina; visual processing.

Zusammenfassung: Sensorische Systeme verteilen eingehende Informationen auf parallele Kanäle. Im visuellen System beginnt dies bereits in der Netzhaut. Dort wird die Bildinformation auf verschiedene Ausgangskanäle verteilt, die jeweils einen bestimmten Satz visueller Merkmale wie Bewegung, Kontrast oder Kanten repräsentieren. In diesem Artikel werden wir die neuesten Erkenntnisse über die funktionelle Organisation des retinalen Ausgangssignals und die neuronalen Mechanismen, die seiner Vielfalt zugrunde liegen, zusammenfassen und erklären wie einzelne visuelle Merkmale, wie Farbe, durch das neuronale Netzwerk der Netzhaut extrahiert werden. Ein tiefes Verständnis davon, wie die Netzhaut – als erste Stufe des visuellen Systems – den visuellen Input filtert, ist ein wichtiger Schritt, um zu verstehen, wie die visuelle Informationsverarbeitung das Verhalten steuert.

Schlüsselwörter: Farbsehen; Retina; visuelle Verarbeitung.

Introduction

The visual system is one of the main senses that animals use in order to navigate in and interact with the world. During the course of evolution, the organization and the function of the visual system underwent constant changes in order to ensure the animal's survival in its natural habitat. For example, the visual system of birds is specialized for high-acuity vision required for prey hunting (Bringmann, 2019), whereas the visual system of rodents is optimized for reliable detection of predators (Johnson et al., 2021).

This visual feature extraction starts in the retina, the first processing stage of the visual system. Across vertebrates, the retinal blueprint is highly conserved (Baden et al., 2020) with five different cell classes (Figure 1a). Photoreceptors convert photons of light into electrical signals. They are divided into two subclasses characterized by different light sensitivity: rods and cones (Lamb, 2016). Photoreceptor signals are modulated by inhibitory feedback from horizontal cells (Chapot et al., 2017), before bipolar cells transfer the visual information to the inner retina. Bipolar cells constitute distinct functional types (Euler et al., 2014) providing the main excitatory drive to retinal ganglion cells (RGCs), the output neurons of the retina. This signal transmission in the inner retina is constantly modulated by the second, most diverse class of inhibitory retinal neurons – amacrine cells (Diamond, 2017). Finally, the visual information is sent to higher visual areas in the brain via the optic nerve.

Since the first functional recordings of retinal neurons many decades ago (Gernandt and Granit, 1947), scientists have been wondering: How does the retina contribute to vision? In other words, what kind of information does the eye send to the brain? Electrophysiological recordings in the frog (Barlow, 1953) and cat (Kuffler, 1953) showed that retinal neurons have antagonistic center-surround receptive fields. It was proposed that this simple receptive field arrangement

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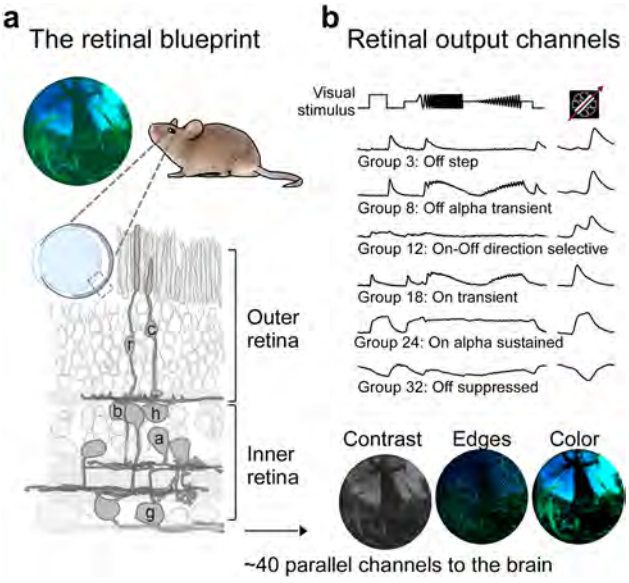

Figure 1: The retina sends parallel visual feature channels to the brain.
(a) Schematic of the retinal blueprint. The visual image is projected onto the retina. Here, the visual signal is detected by photoreceptors (rod [r] and cone [c]) and transferred to ganglion cells (g) via bipolar cells (b). It is modulated by inhibitory horizontal (h) and amacrine (a) cells. **(b)** The output of the retina is functionally diverse (Baden et al., 2016), illustrated by visual responses of exemplary retinal ganglion cell (RGC groups to "chirp" and moving bar stimulus). The chirp stimulus consists of a step of light followed by frequency and contrast modulations to probe the cells' response polarity as well as frequency and contrast preference. Each of the ~40 RGC types in mice encodes specific aspects from the input image, like contrast, edges, or color.

reduces redundancy within the input by spatially decorrelating the visual signal before transmission to the brain (Barlow, 1953; Kuffler, 1953; Srinivasan et al., 1982). However, already in 1959, Lettvin and colleagues (Lettvin et al., 1959) discovered that the optic nerve of the frog constitutes different channels that encode more complex features of the environment. In this way, each of these channels might serve a distinct behavior, like a channel tuned to dark, small moving objects such as a bug may drive prey capture.

In this article, we will summarize research from the last few years on what information the eye sends to the brain and how retinal circuits contribute to visual feature extraction. For that, we will largely focus on work with mice, one of the most frequently used model systems in visual neuroscience, but relate the findings to work on other species.

Organization of the retinal output

The goal of sensory systems is to extract behaviorally relevant features from the environment, thereby building an internal representation of the world. In the visual system, the optic nerve from the eye to the brain constitutes a bottleneck for information transmission. As a result, visual information is already heavily processed in the retina before it is sent to the brain. However, how many RGC types exist and what exactly do they encode? Answering these questions would yield a complete picture of the visual information available to the brain.

The classification of retinal output neurons into different types is an ongoing process and recently advanced with the development of high-throughput techniques for studying morphology, function, and gene expression profiles of retinal cells. Until now, the most comprehensive classification of the retinal output exists in mice. Recent studies based on electron microscopy anatomical reconstructions (Bae et al., 2018), gene expression profiles (Rheaume et al., 2018), and functional properties (Figure 1b; Baden et al., 2016), as well as a combination of all approaches (Goetz et al., 2021), revealed that there are approx. 40 different types of retinal output channels in mice. Interestingly, recent evidence suggests that the number of RGC types is comparable across other vertebrate species (Baden et al., 2020): Single-cell RNA sequencing revealed 41 RGC types in the chicken retina (Yamagata et al., 2021) and more than 30 RGC types in the zebra fish retina (Kölsch et al., 2021). This indicates that splitting the visual input into many retinal output channels is a common strategy across, at least some, vertebrate species. But what exactly do single (mouse) RGC types encode? Each RGC type can be characterized by its response profile to visual stimulation, as it is selective for specific features of the visual input. For example, the On-Off "W3" RGC type is sensitive to local motion acting as a local edge detector (Zhang et al., 2012), and the On-Off direction-selective RGCs encode the direction of motion. To what extent single RGC types contribute to distinct behaviors – as suggested by Lettvin and colleagues in the frog (Lettvin et al., 1959) – remains unclear. Recently, a direct link between RGC function and behavior has been demonstrated for looming-evoked flight response in mice (Johnson et al., 2021) and phototactic behavior in zebra fish (Yoshimatsu et al., 2020). However, this high-level function of retinal output channels likely does not apply to most RGC types, as this would make behavior relatively inflexible.

Mechanisms contributing to the functional diversity of retinal circuits

The great functional diversity of cell types at the level of the retinal output is astonishing, given the fact that there are just a handful of cell types with only two synapses upstream. This raises the important question about how

the diversity of the population of RGC types is generated within the retinal network? In the following, we will review a few recent studies addressing this topic.

Amacrine cells are the most diverse class of retinal neurons and likely play a critical role in all feature-extracting retinal circuits (Diamond, 2017). For example, starburst and wide-field amacrine cells are involved in generating direction selectivity (Euler et al., 2002) and segregating object from background-motion (Olveczky et al., 2003). Moreover, a study based on population recordings of all bipolar cell types revealed a general role of amacrine cells in retinal processing: To decorrelate excitatory channels across different cell types (Figure 2a; Franke et al., 2017). Specifically, pharmacological experiments showed that GABA-ergic wide-field amacrine cells provide decorrelating inhibition to bipolar cells, gated by glycinergic small-field amacrine cells. These findings suggest that inhibition significantly contributes to the generation of diverse excitatory channels in the retina.

Next to inhibition, cell-intrinsic properties contribute to the diversification of visual signals. In general, we still know relatively little about how intrinsic properties contribute to retinal processing. However, it was recently shown that different RGC types differ with respect to dendritic integration of synaptic inputs due to cell type-specific morphology and ion-channel complement (Figure 2b; Ran et al., 2020). This likely results in a different stimulus selectivity of these RGC types, despite the fact that they share some excitatory input. Moreover, another new study investigating RGC spike generation showed that type-specific expression of voltage-gated ion-channels results in functional differences between RGC types (Wienbar and Schwartz, 2021).

The retinal output signal can also be shaped in a type-specific manner by neuromodulation. In contrast to neurotransmitters, neuromodulators act over long distances and their effect can be maintained over long timescales (Hyman, 2005). So far, the function of only some of these compounds has been explored in the retina. For example, studies on dopamine and nitric oxide revealed that they control electrical coupling via gap junctions that changes the network excitability (Jacoby et al., 2018; Mills and Massey, 1995). It was shown that both of these neurotransmitters are engaged in controlling the transition between rod- and cone-dominated circuits. Interestingly, a recent *in vivo* study in mice suggests that the retinal output is also modulated by the animal's arousal state (Schröder et al., 2020). In mammals, there are few projections from

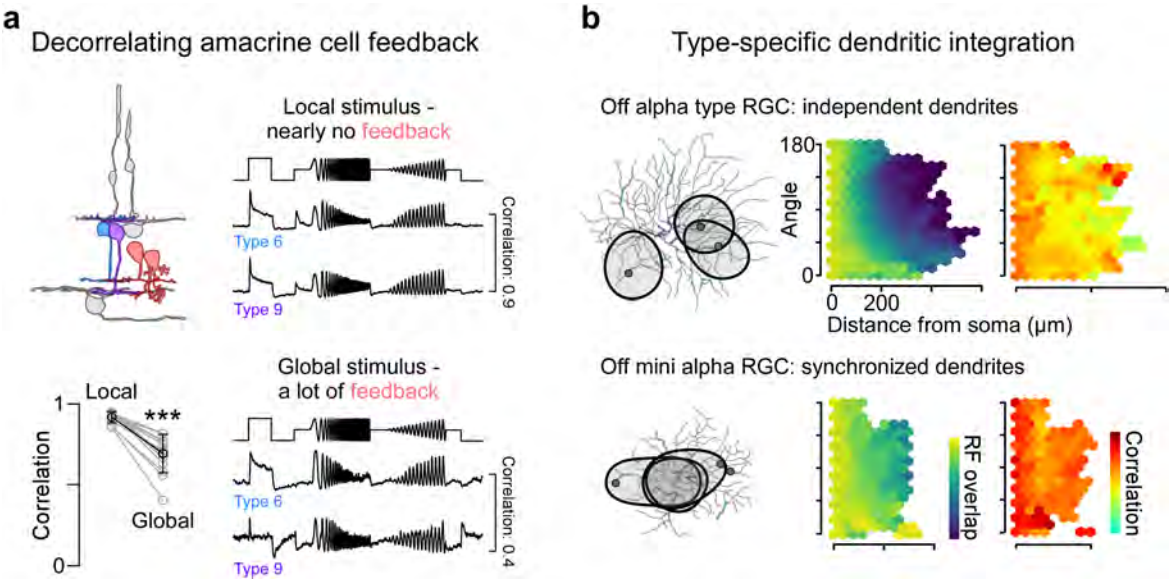

Figure 2: Mechanisms contributing to a functionally diverse retinal output.
(a) Inhibitory feedback from amacrine cells decorrelates bipolar cell types in the mouse retina (Franke et al., 2017). Top left: Schematic of retinal cell classes, with two types of bipolar (blue and violet) and amacrine cell (red). Top right: Mean visual responses of type 6 and 9 bipolar cell in response to a local chirp stimulus, eliciting weak feedback from amacrine cells and resulting in highly correlated responses across types. Bottom right: Same as before, but in response to a global stimulus that evokes strong amacrine cell feedback and results in lower response correlations – a general mechanism across all bipolar cell types, as depicted in the bottom left. **(b)** Type-specific dendritic integration profiles of RGCs result in different integration of synaptic inputs (Ran et al., 2020). Top row: reconstructed dendritic morphology of off-alpha-type RGC with outlines of three dendritic receptive fields (RFs; left) and RF overlap (middle) and temporal correlation of chirp responses (right) as a function of dendritic distance to soma and angle between dendritic regions. Bottom row shows the same, but for off-mini apha RGC. While off-alpha cells have isolated dendrites with little RF overlap and low correlations, off-mini alpha RGCs exhibit highly synchronized dendrites.

the brain to the retina, such as histaminergic fibers from hypothalamus or serotonergic fibers from the dorsal raphe (Gastinger et al., 2006). Therefore, these top-down neuromodulatory connections acting on specific RGC types might further increase the complexity of the retinal output. Such neuromodulatory effects of retinal processing by other brain areas are well-described in other vertebrate species like zebra fish (Corradi and Filosa, 2021) and birds (Wilson and Lindstrom, 2011).

Following single visual features across the retinal network

Despite our detailed understanding of the organization of the retinal output and, more generally, retinal cell types, we still know relatively little about how the selectivity for single visual features arises within the retinal network. For that, it is critical to follow its neural representation across consecutive retinal processing levels. Here, color represents an ideal visual feature to study, as it is an important aspect of natural scenes relevant for distinct behaviors (Gerl and Morris, 2008), and it can be experimentally targeted by stimulus design. The neural basis of color vision relies on the presence of at least two photoreceptor types tuned to different wavelengths, and their output signals have to be compared along downstream (retinal) pathways.

Mice are dichromats and possess two types of cones (Jacobs et al., 1991). S-cones expressing UV-sensitive S-opsins are distributed across the whole retina (Haverkamp et al., 2005), with higher density in the ventral part (Nadal-Nicolás et al., 2020). M-cones express green-sensitive M-opsins in the dorsal retina and coexpress S-opsin toward the ventral part (Baden et al., 2013; Röhlich et al., 1994). This asymmetric opsin-expression profile also exists in other species like guinea pig and hyenas (Peichl, 2005) and likely represents an adaptation to the statistics of natural scenes (Baden et al., 2013). Although this opsin distribution was long believed to be detrimental to local comparisons of spectral signals required for color vision, now there is behavioral evidence demonstrating that mice are able to discriminate different colors (Jacobs et al., 2004) – at least in the upper visual field (Denman et al., 2018). Yet, what retinal mechanism could mediate chromatic processing restricted to the upper visual field?

By combining population two-photon imaging from photoreceptors all the way to the retinal output with chromatic stimulation (Franke et al., 2019), a recent study (Szatko et al., 2020) revealed that most color-opponent neurons – preferring an antagonistic stimulus in the UV and green channel – are located in the ventral retina in mice (Figure 3a). Importantly, color-opponency was already established at the level of the cone output, likely originating from rod photoreceptors and involving horizontal cell feedback. This mechanism was already proposed in an earlier study identifying color-opponency in a genetically identified RGC type (Joesch and Meister, 2016). These findings are in line with a recent electrophysiological study showing that RGC nonlinear chromatic integration is restricted to the ventral retina involving both rods and cones, which might facilitate the encoding of the horizon (Khani and Gollisch, 2021). Interestingly, rod–cone opponency might also underlie color vision in monochromatic human patients that have only blue-sensitive cones and rods (Reitner et al., 1991). As rods might escape saturation upon higher light levels in mice (Tikidji-Hamburyan et al., 2017), rod–cone opponency might also contribute to color vision under daylight conditions. Until now, it is still unclear to what extent cone-based color vision well-described in primates exists in mice (but see Mouland et al., 2021; Stabio et al., 2018).

In general, the consistent finding that color-opponency is largely restricted to the ventral retina in mice is in line with a behavioral study showing that mice are best at discriminating different colors in the upper visual field (Denman et al., 2018) that is encoded by the ventral retina. Importantly, statistical analysis of natural images captured in the environment of mice using a custom-built camera revealed an abundance of color contrast for elevations above the horizon (Figure 3b; Abballe and Asari, 2021). This suggests that the asymmetric processing of color information across the mouse retina might represent an adaptation to the distribution of color contrasts in natural scenes. So far, the relevance of mouse color vision for distinct behaviors is still unclear. However, one might speculate that color vision in the upper visual field will facilitate the detection of predators approaching from above by increasing contrast in the sky.

Summary and outlook

In this article, we reflected on recent findings regarding how visual feature extraction in the retina contributes to visual processing. As the visual system of different animal species is adapted to the statistics of their natural environment (Baden et al., 2020), a critical next step for understanding visual circuit function is to use more complex and natural visual stimuli. While simple, parametric stimuli are easy to control, and corresponding responses are straightforward to interpret, they largely allow studying

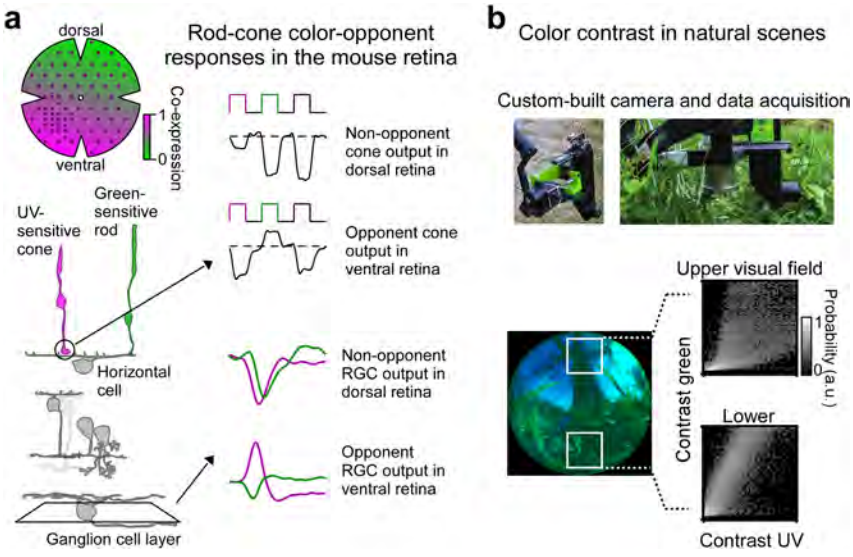

Figure 3: Chromatic processing in the mouse retina and natural scene statistics.
(a) Rod–cone color-opponent responses in the ventral mouse retina (Szatko et al., 2020). Top left: Distribution of S-cones (dots) and expression of S- and M-opsin in M-cones across the retina. Right: Examples of cone responses to UV and green full-field flashes (top) and preferred UV and green stimuli of RGCs in the dorsal and ventral retina. **(b)** Color contrast is enriched in the upper visual field of mouse natural scenes (Qiu et al., 2021). Images of custom-built camera (top) and example scene with contrast distributions of upper and lower visual field (bottom).

responses to single or few visual features. By contrast, natural scenes contain richer, higher order spatiotemporal statistics, such as global and local motion as well as correlations in space and time (Kayser et al., 2003; Nitzany and Victor, 2014; Rikhye and Sur, 2015; Simoncelli and Olshausen, 2001; Tanaka et al., 2009). Importantly, neural responses systematically change with a more naturalistic input (David et al., 2004; Froudarakis et al., 2014).

Using naturalistic stimuli for studying visual processing, however, is associated with technical challenges: Neural responses to naturalistic stimuli are often difficult to interpret using conventional analysis methods like spike-triggered averaging for receptive field estimation (Chichilnisky, 2001). Here, more powerful models, such as deep neural networks, offer faithful response predictions to arbitrary stimuli including natural scenes (McIntosh et al., 2016; Vintch et al., 2015). This promises to identify the neurons' feature selectivity in the context of a natural input, which will greatly facilitate our understanding of how visual processing relates to behavior – a still open question in neuroscience.

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Bionotes

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Review article

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Emergence of synaptic organization and computation in dendrites

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Abstract: Single neurons in the brain exhibit astounding computational capabilities, which gradually emerge throughout development and enable them to become integrated into complex neural circuits. These capabilities derive in part from the precise arrangement of synaptic inputs on the neurons' dendrites. While the full computational benefits of this arrangement are still unknown, a picture emerges in which synapses organize according to their functional properties across multiple spatial scales. In particular, on the local scale (tens of microns), excitatory synaptic inputs tend to form clusters according to their functional similarity, whereas on the scale of individual dendrites or the entire tree, synaptic inputs exhibit dendritic maps where excitatory synapse function varies smoothly with location on the tree. The development of this organization is supported by inhibitory synapses, which are carefully interleaved with excitatory synapses and can flexibly modulate activity and plasticity of excitatory synapses. Here, we summarize recent experimental and theoretical research on the developmental emergence of this synaptic organization and its impact on neural computations.

Keywords: cortex; dendrite; development; organization; synaptic plasticity.

Zusammenfassung: Einzelne Neuronen im Gehirn weisen erstaunliche Rechenfähigkeiten auf, die sich im Laufe der Entwicklung allmählich entwickeln und es den Neuronen ermöglichen, in komplexe neuronale Schaltkreise integriert zu werden. Diese Fähigkeiten leiten sich unter anderem von der genauen Anordnung der Synapsen auf den Dendriten der Neuronen ab. Während der genaue rechnerische Nutzen dieser Anordnung noch unbekannt ist, zeichnet sich ein Bild ab, in dem Synapsen nach ihren funktionellen Eigenschaften über mehrere räumliche Ebenen hinweg organisiert sind. Während auf der lokalen Ebene (zehn Mikrometer) exzitatorische synaptische Eingänge dazu neigen, Cluster entsprechend ihrer funktionalen Ähnlichkeit zu bilden, zeigen synaptische Eingänge auf der Ebene einzelner Dendriten oder des gesamten Baums "dendritic maps", bei denen die Funktion exzitatorischer Synapsen gleichmäßig mit der Position auf dem Dendriten variiert. Die Entwicklung dieser Organisation wird durch inhibitorische Synapsen unterstützt, die präzise mit exzitatorischen Synapsen verflochten sind und die Aktivität und Plastizität exzitatorischer Synapsen flexibel modulieren können. Hier fassen wir aktuelle experimentelle und theoretische Forschung über die Entstehung dieser synaptischen Organisation in der Entwicklung und ihren Einfluss auf neuronale Berechnungen zusammen.

Schlüsselwörter: Kortex; Dendrit; Entwicklung; Organisation; synaptische Plastizität.

Introduction

Neurons process information in the form of electrical signals called action potentials. These signals are transmitted via synapses from one neuron to another. At a synapse, an electrical signal induces the release of neurotransmitters which affect the receiving neuron's membrane potential. The majority of synapses are found on dendrites, branch-like extensions of a neuron that receive electrical stimulation from other neurons and carry it to the neuron's cell body called the soma. Depending on the neurotransmitter a synapse releases, a synapse is either excitatory, i.e., usually depolarizing the membrane potential via the release of acetylcholine or glutamate, or inhibitory, i.e., usually hyperpolarizing the membrane potential via the release of gamma-aminobutyric acid (GABA) or glycine. The exact arrangement of excitatory and inhibitory synapses influences the generation of action potentials at the soma,

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and hence the transmission of information to other neurons, and is of central importance for information processing in the brain (Stuart et al., 2016).

During early development, various single neuron and neural circuit properties, such as the organization of synapses, emerge through the interaction of multiple factors, including genetically regulated cell specification and activity-dependent circuit formation and refinement. Since many of the sensory organs in the developing brain are immature, much of the early neural activity is generated *spontaneously* in the absence of sensory stimulation. Almost all neural circuits in the developing brain can generate spontaneous activity, including the sensory cortex on which we focus here (Leighton and Lohmann, 2016). Spontaneous activity is usually highly structured and contains spatiotemporal correlations to instruct the formation, the removal, and the changes in strength of synaptic inputs. The developing retina exhibits one of the best studied examples of spontaneous activity known as retinal waves, which directly influence connectivity refinement and receptive field tuning in downstream visual areas such as the superior colliculus and the thalamus (Blankenship and Feller, 2010). Specific activity-dependent plasticity mechanisms drive this connectivity refinement (Richter and Gjorgjieva, 2017). The exact form of these plasticity mechanisms and their functional implications are an active area of research (Agnes and Vogels, 2021; Hiratani and Fukai, 2018; Kirchner and Gjorgjieva, 2021; Mikulasch et al., 2021; Sezener et al., 2021).

There are different computational and theoretical approaches to investigate the emergence of organization in the developing brain. In one approach, neurons are modeled as so-called *point neurons* that conceptualize neurons as single points without spatial extent. Often, point neurons are assumed to directly integrate synaptic inputs and transform them into spiking outputs while ignoring the transformations implemented by dendrites. Point neurons have the advantage that they are amenable to mathematical analysis while still capturing the ability of the neuron to generate action potentials and can be easily connected when simulating large networks. At the other end of the spectrum, multicompartment neuron models include fully reconstructed dendrites to carefully incorporate the influence on the soma of individual synaptic inputs across the dendritic tree. Multicompartment models are often equipped with a variety of ion channels, allowing them to produce a wide range of local, nonlinear transformations of the input. While these models are typically mathematically intractable, they reveal the profound impact of synapses' distribution on dendritic, cellular, and network computations and neural information processing more generally (Poirazi et al., 2003).

Here, we adopt a third perspective, similar to the passive multicompartment model, in which we retain the dendrite's shape while abstracting away many details of a full biophysical model. We distinguish between different spatial scales of synaptic organization on a dendrite, local and global, and summarize recent experimental and theoretical progress on understanding the properties, functions, and developmental emergence of this organization. We highlight differences and commonalities between excitatory and inhibitory synapse organization and possible functional consequences of their interaction. Finally, based on experimental data from the developing retina, we propose a model for the developmental emergence of balanced excitation and inhibition.

Organization of excitatory synapses

Most of the synaptic inputs that reach a neuron arrive on its dendrites. How these signals are integrated and finally transformed into action potentials is of central importance for understanding neuronal information processing (Spruston et al., 2016). Dendrites can support information processing at multiple spatial scales (Figure 1). On the local scale, i.e., the fine-scale organization of synapses over tens of microns, dendrites affect information processing by organizing synapses with similar properties into *synaptic clusters* that boost a neuron's computational capacity through nonlinear integration (Kastellakis et al., 2015; Mel, 1992, 1993; Poirazi et al., 2003; Ujfalussy and Makara, 2020; Wilson et al., 2016). On the level of

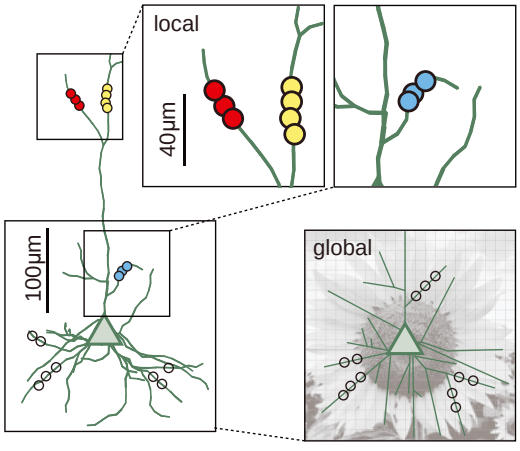

Figure 1: A schematic of a dendrite with synapses (colored dots). Synapses exhibit organization at multiple spatial scales. At the local scale of tens of microns (top right), synapses form clusters in which synapses with similar selectivity (indicated by the color) are in spatial proximity. At the global scale (bottom right), synapses form dendritic maps, where nearby locations in visual space, represented by the sunflower, are encoded by synapses at nearby locations on the dendrite (black circles).

individual branches, dendrites exhibit *dendritic maps* in which the tuning of synapses (or synaptic clusters) varies systematically across the dendritic tree (Bollmann and Engert, 2009; Iacaruso et al., 2017; Jia et al., 2014; Podgorski et al., 2021; Wilson et al., 2016). Finally, the dendrite's branching structure determines the extent to which synaptic inputs influence the soma (Ferrante et al., 2013; Jaffe and Carnevale, 1999; Tzilivaki et al., 2019; Vetter et al., 2001).

There is accumulating evidence that a substantial amount of the dendritic organization across these scales emerges already during early development (Kirchner and Gjorgjieva, 2021; Kleindienst et al., 2011; Lee et al., 2016; Niculescu et al., 2018; Takahashi et al., 2012; Winnubst et al., 2015). This early emergence is particularly noteworthy as neural activity during these early phases primarily arises spontaneously (Leighton and Lohmann, 2016), raising the question of how the brain can precisely arrange synaptic inputs across scales without sensory input. Investigating this question reveals essential facts about the mechanisms of brain development and provides a valuable perspective on how the adult brain works.

Synaptic clustering

In the case of local organization, synapses onto mouse pyramidal neurons arrange into clusters during early postnatal development (Kleindienst et al., 2011; Niculescu et al., 2018; Takahashi et al., 2012; Winnubst et al., 2015) (Figure 2a). Clustering refines over development (Takahashi et al., 2012) and cannot form when spontaneous activity is absent (Kleindienst et al., 2011; Takahashi et al., 2012). Further, experiments blocking individual molecules and their receptors implicate a family of signaling molecules called *neurotrophic factors* in this process (Kutsarova et al., 2021; Niculescu et al., 2018; Winnubst et al., 2015). Computational modeling demonstrates that the interactions between these neurotrophic factors effectively implement a local plasticity rule that can generate clustering (Kirchner and Gjorgjieva, 2021), where poorly synchronized synapses weaken and well-synchronized synapses stabilize (Niculescu et al., 2018; Winnubst et al., 2015). As the activity becomes driven by the senses and the animal encounters more complex situations, the substrate of plasticity becomes more complex over development. While the prevalence of the relevant

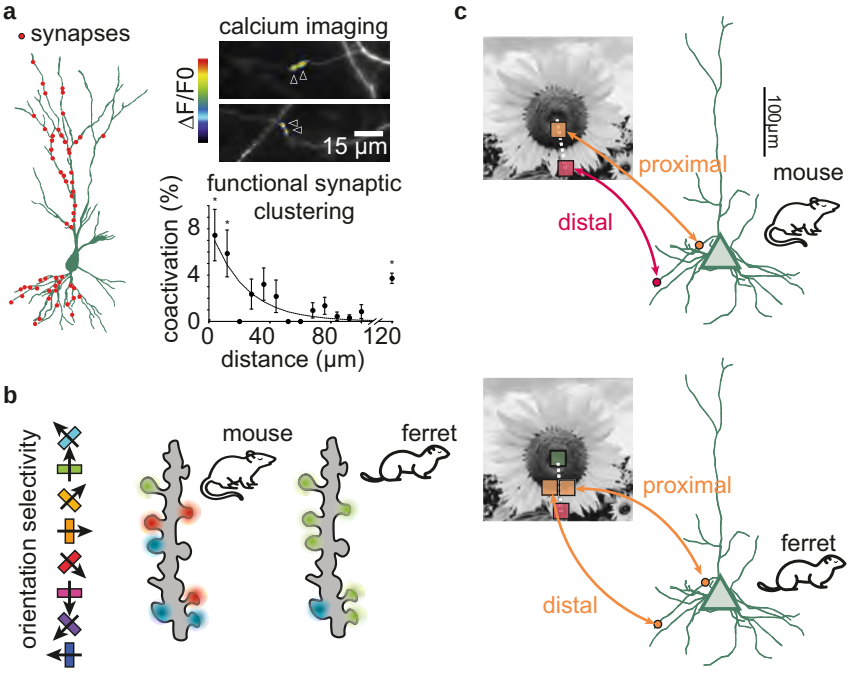

Figure 2: Species-specific local and global organization of excitatory synapses.
(a) Left: reconstruction of a CA3 pyramidal neuron with synaptic inputs indicated as red circles. Redrawn from ref (Kleindienst et al., 2011). Top right: calcium activity in clustered synaptic inputs in developing CA3 pyramidal cell dendrites. Redrawn from ref (Niculescu et al., 2018). Bottom right: synaptic coactivation as a function of intersynaptic distance. Redrawn from ref (Kleindienst et al., 2011). **(b)** Illustration of qualitatively different types of clustering in mouse and the ferret: the ferret shows clustering according to orientation, whereas the mouse does not and instead shows clustering according to receptive field overlap (Iacaruso et al., 2017; Wilson et al., 2016). **(c)** Illustration of a retinotopically organized dendritic map observed in the mouse (top) but not in the ferret (bottom).

neurotrophic factors decreases with age (Yang et al., 2009), there is evidence that the local plasticity rule also applies in the adult animal, possibly implemented by different sets of interacting molecules (El-Boustani et al., 2018; Harward et al., 2016; Hedrick et al., 2016; Oh et al., 2015; Tazerart et al., 2020). This parallel hints at the exciting possibility that the underlying principles of synaptic plasticity remain unchanged and form a foundation for more versatile plasticity during adult life (Ganguly and Poo, 2013; Lohmann and Kessels, 2014).

While synaptic clustering appears to be near-ubiquitous across brain areas and species (Adoff et al., 2021; Ashaber et al., 2021; Frank et al., 2018; Fu et al., 2012; Gökçe et al., 2016; Iacaruso et al., 2017; Ju et al., 2020; Kerlin et al., 2019; Kim et al., 2021; Kleindienst et al., 2011; Lee et al., 2019; McBride et al., 2008; Niculescu et al., 2018; Podgorski et al., 2021; Scholl et al., 2017; Takahashi et al., 2012; Wilson et al., 2016; Winnubst et al., 2015), there is striking variability in the qualitative characteristics of clusters. The receptive field of a synapse – the sensory feature encoded by the synaptic input – can be used to describe the properties of clusters. For example, synaptic clusters in the ferret or macaque visual cortex tend to have receptive fields that share a preference for moving gratings of the same orientation (Scholl et al., 2017; Wilson et al., 2016). This shared orientation preference is not present in the mouse visual cortex, where instead, synapses with spatially overlapping receptive fields tend to form a cluster (Iacaruso et al., 2017; Jia et al., 2010) (Figure 2b). Computational modeling demonstrates that the differences between the mouse, ferret, and macaque visual cortex might result from two simple factors: the anatomical size of the retina and the anatomical size of the visual cortex (Kirchner and Gjorgjieva, 2021; Scholl et al., 2017).

Thus, central aspects of the local synaptic organization can emerge without sensory stimulation, suggesting that development might equip dendrites with fundamental building blocks such as feature selectivity from which other functional properties derive in adulthood. Computational modeling stands out as a handy tool for investigating this hypothesis, as longitudinal experiments that monitor synaptic organization and function across development and into adulthood (Witvliet et al., 2021) are currently technically infeasible.

Dendritic maps

Beyond the fine-scale organization over tens of microns, there is also accumulating evidence for synaptic organization on the level of entire dendritic branches (hundreds of microns). Concretely, synapses do not only cluster locally but also tend to organize along the entire dendritic tree, according to their function (Bollmann and Engert, 2009; El-Boustani et al., 2018; Iacaruso et al., 2017; Jia et al., 2014; Kerlin et al., 2019; Podgorski et al., 2021; Wilson et al., 2016). One striking example of this can be observed in the *Xenopus* tadpole tectum (Bollmann and Engert, 2009) and in the mouse visual cortex (El-Boustani et al., 2018; Iacaruso et al., 2017) where synapses are arranged retinotopically, i.e., proximal (distal) synapses tend to respond to stimulation of central (peripheral) locations in visual space (Figure 2c). We note, however, that the existing experimental data in the mouse and ferret visual cortex do not provide information about the relationship between synapse proximity and location on basal versus apical dendrites. A similar synaptic organization can be observed in the mouse barrel cortex, where proximal (distal) synapses tend to respond (not respond) to stimulation of the primary whisker of the corresponding barrel (Jia et al., 2014; Schoonover et al., 2014), and in the hippocampus, where individual branches respond to specific locations in space (Rashid et al., 2020). We term this type of global organization *dendritic maps* (Kirchner and Gjorgjieva, 2021) to highlight the similarity with *cortical maps* (White and Fitzpatrick, 2007). In the ferret visual cortex, this retinotopic organization is markedly absent (Scholl et al., 2017) (Figure 2c), and instead, synapses on the same dendritic branch tend to share the same preference for oriented gratings (Wilson et al., 2016).

While experimental evidence for dendritic maps abounds, their possible function is mostly unclear. One explanation for why different dendritic branches receive different inputs is that this separation allows the soma to weigh the inputs according to their reliability, enabling Bayes-optimal integration (Jordan et al., 2021). Alternatively, different dendritic branches might be gated on or off in a context-dependent fashion (Yang et al., 2016), allowing more powerful dendritic computations (Poirazi et al., 2003) and modifying only a subset of synapses while retaining the rest (Cichon and Gan, 2015; Sezener et al., 2021; Yaeger et al., 2019). A third hypothesis is that the feature selectivity of different synapses matches commonly co-occurring features in complex sensory inputs, allowing the neuron to perform more efficient feature detection (Hiratani and Fukai, 2018; Iacaruso et al., 2017; Kirchner and Gjorgjieva, 2021). Finally, the ability of dendrites to segregate feed forward and feedback information into different compartments (Larkum et al., 2009; Takahashi et al., 2016) might provide a biological substrate for

determining the contribution of individual inputs to the outcome of a computation, known as the credit assignment problem (Guerguiev et al., 2017; Richards and Lillicrap, 2019).

However, recent experiments have revealed that our understanding of dendritic computations is still limited. The somatic receptive field seems to be derived from only a handful of powerful synaptic connections (Cossell et al., 2015). Indeed, removing the entire basal or apical dendrites *in vivo* does not affect the functional selectivity of the soma (Park et al., 2019). Also, large dendritic events *in vivo* overwhelmingly co-occur with somatic events in typical recording setups (Beaulieu-Laroche et al., 2019; Francioni et al., 2019; Kerlin et al., 2019) and only become substantially decoupled when the animal is allowed to move freely (Voigts and Harnett, 2020). These observations indicate that proper investigation of structured and diverse synaptic input across the entire dendritic tree might require a richer set of stimuli (Laboy-Juárez et al., 2019) that engages the full cognitive potential of the animal.

How might dendritic maps be established? In contrast to synaptic clustering, there is only limited experimental evidence of the presence of dendritic maps in early development (Bollmann and Engert, 2009). Computational modeling suggests that local, structural plasticity in conjunction with an attenuating back-propagating action potential is sufficient to produce species-specific dendritic maps (Kirchner and Gjorgjieva, 2021). Alternatively, (Hiratani and Fukai, 2018) propose that dendritic maps might also arise during development from a combination of plasticity that depends on the location of the synapse on the dendritic tree (Froemke et al., 2005; Letzkus et al., 2006; Weber et al., 2016) and structural synaptic rewiring (Mel, 1992). Finally, recent experimental data demonstrate that dendritic growth is affected by synaptic activity (Podgorski et al., 2021), suggesting that changes to dendritic morphology might facilitate dendritic map formation. Since early development is characterized by the establishment of dendritic morphology (Richards et al., 2020) and by repeated and rapid synapse turnover (Holtmaat and Svoboda, 2009; Maletic-Savatic et al., 1999), it appears as a particularly opportune time for the formation of dendritic maps.

In summary, there is accumulating evidence that dendrites exhibit dendritic maps, i.e., topographically organized synaptic inputs across the entire dendritic tree. These dendritic maps exhibit substantial qualitative variability across areas and species. While their function is still unclear, computational models generate several testable predictions and provide hypotheses that can guide the direction of future experimental research.

Organization of inhibitory synapses

Most studies on synaptic organization focus on excitatory synapses. This focus is traditionally attributable to the relative abundance of glutamatergic synapses and the better availability of markers for glutamatergic synapses (Chen et al., 2012). Even though inhibitory synapses, which represent 12% of all dendritic synapses (Iascone et al., 2020), have been relatively neglected by comparison, they play an essential role in neural information processing (Boivin and Nedivi, 2018).

Local balance of excitatory and inhibitory synapses

The balance of excitation and inhibition is a characteristic feature of cortical dynamics (Okun and Lampl, 2008). Still, it is an open question on just how *detailed* this balance is (Hennequin et al., 2017): does the balance extend to the dendritic tree, individual branches, or even local stretches on the dendrite (Figure 3a)? These questions are the center of new experimental studies on inhibitory synapse organization and dynamics.

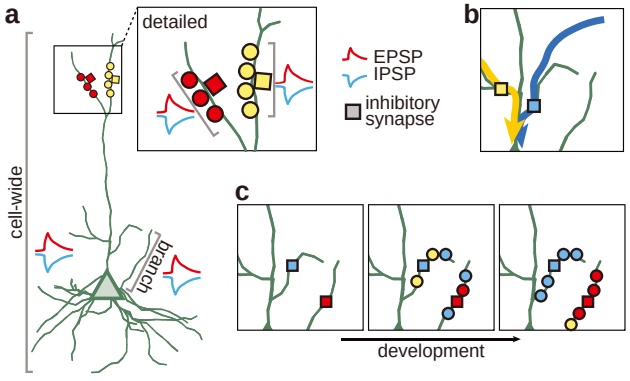

Figure 3: Function and origin of locally balanced excitation and inhibition.
(a) Illustration of the balance of excitation and inhibition at different spatial scales. Balance might exist cell-wide (excitation and inhibition matched at the soma), on individual branches, or local stretches of the dendrite (detailed balance, inset, top right). **(b)** Inhibitory synapses (colored squares) might gate dendritic signals by selectively inhibiting some branches but not others (Boivin and Nedivi, 2018). Yellow and blue arrows indicate incoming signals from two different branches. **(c)** Model of the emergence of excitatory and inhibitory balance over development, based on experiments in the mouse retina (Bleckert et al., 2013; Johnson et al., 2003; Soto et al., 2011). Inhibitory synapses form first (left) and provide a scaffold around which excitatory synapses organize (middle). Structural and functional plasticity rearranges excitatory synapses to establish a detailed dendritic balance (right).

On the local scale, inhibitory synapses exhibit a substantial amount of organization (Chen et al., 2012; Iascone et al., 2020; Liu, 2004; Villa et al., 2016). In contrast to excitatory synapses, which primarily reside on dendritic spines, inhibitory synapses can be found both on spines and the dendritic shaft (Iascone et al., 2020). The density of inhibitory synapses closely tracks the density of excitatory synapses (Iascone et al., 2020), and 25–30% of all inhibitory synapses share a dendritic spine with an excitatory synapse (Chen et al., 2012; Iascone et al., 2020), an arrangement called *dually innervated spines*. Excitatory synapses on dually innervated spines are extraordinarily stable and experience almost no turnover (Villa et al., 2016). By contrast, inhibitory synapses on dually innervated spines experience increased remodeling, repeatedly appearing and disappearing on the same spine (Villa et al., 2016). Experimental stimulation of clustered excitatory synapses triggers the *de novo* formation of inhibitory synapses (Hu et al., 2019). Also, during normal visual experience, whenever excitatory synapses are stable, nearby inhibitory synapses within 10 μm are also stable (Chen et al., 2012). Finally, experiments in a hippocampal culture provide evidence for a push–pull plasticity mechanism that can carefully balance excitatory and inhibitory strength (Liu, 2004). Thus, a detailed balance of excitation and inhibition on local stretches of dendrites appears entirely consistent with the experimental data.

Based on their location on specific parts of the dendritic tree, inhibitory synapses can effectively shape dendritic signal detection and integration by restricting both voltage and calcium signaling of excitatory synapses (Boivin and Nedivi, 2018; Higley, 2014; Liu, 2004) (Figure 3b). Computational modeling proposes several possible benefits of this property of inhibitory synapses. Consistent with experiments (Wang and Maffei, 2014), modulating local inhibition can change the shape of the learning rule for excitatory synapses (Agnes and Vogels, 2021; Hiratani and Fukai, 2017; Mikulasch et al., 2021). Based on the relative timing and strength of the inhibitory input, potentiation and depression of excitatory synapses can be attenuated (Agnes and Vogels, 2021) or even fully inverted (Hiratani and Fukai, 2017; Mikulasch et al., 2021). This inhibitory control over excitatory plasticity might enable the recalibration of selectivity of excitatory synapses in the visual cortex when input from one eye is lost (Hiratani and Fukai, 2017). Alternatively, local inhibition can help to avoid redundancies in the neural code and lead to more efficient and diverse feature representations (Mikulasch et al., 2021). Finally, gating excitatory plasticity through local inhibition can allow for the rapid reorganization of excitatory synapses during periods of disinhibition, while keeping excitatory organization stable (Agnes and Vogels, 2021; Sezener et al., 2021).

How a highly detailed balance of excitation and inhibition emerges in the cortex is still an open question, but studying the emergence of detailed balance in the mouse retina (Bleckert et al., 2013; Jain et al., 2020; Johnson et al., 2003; Soto et al., 2011) might provide important insights. In the retina, inhibitory synapses form slightly before excitatory synapses (Johnson et al., 2003); the density of both types of synapses increases gradually until eye opening (Soto et al., 2011); and excitatory synapses are more likely to form nearby inhibitory synapses (Bleckert et al., 2013). These constraints postulate a model in which inhibitory synapses form a stable backbone around which excitatory synapses cluster (Kirchner and Gjorgjieva, 2021). Once the density of excitatory and inhibitory synapses has stabilized, a local plasticity rule can further rearrange synapses and establish synaptic clusters to enable flexible computations and efficient learning (Agnes and Vogels, 2021; Hiratani and Fukai, 2017; Kirchner and Gjorgjieva, 2021; Mikulasch et al., 2021) (Figure 3c).

While less is known about the organization of inhibitory synapses than of excitatory synapses, recent experiments and modeling studies paint a picture in which both types of synapses interact closely. Inhibitory synapses can exercise tight control over excitatory activity and plasticity, allowing for more flexible and diverse neural computations. During development, inhibitory synapses might form a backbone that substantially constrains and guides the emergence of excitatory synapse organization.

Discussion

The precise organization of synapses across the dendritic tree makes us hopeful that the daunting amount of detail present in biological dendrites as the branches that enable neurons to connect and transmit information might eventually lead to the discovery of unifying principles. Synaptic clustering, dendritic maps, and detailed excitatory–inhibitory balance all share the hallmark features of organization of the cortex at large: nearby neurons tend to share functional properties (Dombeck et al., 2009), neurons across the cortical sheet arrange into cortical maps (White and Fitzpatrick, 2007), and excitatory and inhibitory activity at the level of the soma is balanced (Okun and Lampl, 2008). We are excited to see if further parallels will emerge as experimental methods become more powerful (Podgorski et al., 2021).

While we focused on the organization of synapses on dendrites, conversely, dendrites' shape is affected by the availability of suitable synaptic partners (Niell et al., 2004; Podgorski et al., 2021; Stuart et al., 2016). As a consequence, a mature dendrite's shape might not only affect its possible inputs and thereby its computational capacities but also be the result of activity-dependent plasticity processes during early development. A time-lapsed optical imaging of dendrite growth during spontaneous activity or in conjunction with sensory stimulation (Podgorski et al., 2021) will be able to ascertain the degree to which activity affects dendrite growth and vice versa.

A wide range of further distinctions is possible beyond the broad separation of synapses into excitatory and inhibitory. Inhibitory interneurons fall into several genetically characterized subtypes, which differ in their biophysical properties and subcellular specificity (Tremblay et al., 2016). While fast-spiking, parvalbumin-positive interneurons tend to form synapses onto the soma and the proximal dendrite, other interneuron types prefer the distal basal or the apical tuft. While research on circuit implications of interneuron diversity is well underway, functional implications of different interneuron subtypes on different parts of the dendrite are only just shifting into focus (Vercruysse et al., 2021).

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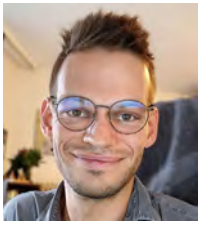
Bionotes



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Review article

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Brain–body communication in stroke

Mens sana in corpore sano

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Abstract: Stroke is a leading cause of death and disability worldwide with limited therapeutic options available for selected groups of patients. The susceptibility to stroke depends also on systemic parameters, and some stroke risk factors are modifiable, such as atrial fibrillation (AF) or hypertension. When considering new treatment strategies, it is important to remember that the consequences of stroke are not limited to the central nervous system (CNS) injury, but reach beyond the boundaries of the brain. We provide here a brief overview of the mechanisms of how the brain communicates with the body, focusing on the heart, immune system, and gut microbiota (GM).

Keywords: brain hemorrhage; gut microbiota (GM); heart; immune system; ischemic stroke.

Zusammenfassung: Schlaganfall ist weltweit eine der häufigsten Ursachen für Tod und Behinderungen, wobei nur limitierte Therapieoptionen für bestimmte Patientengruppen zur Verfügung stehen. Ob ein Mensch anfällig für einen Schlaganfall ist, hängt auch von systemischen Parametern ab und einige Risikofaktoren für Schlaganfall lassen sich beeinflussen, wie z. B. Vorhofflimmern oder Bluthochdruck. Bei der Erwägung neuer Behandlungsstrategien ist es wichtig zu bedenken, dass die Folgen eines Schlaganfalls nicht auf den zentralnervösen Schaden beschränkt sind, sondern über die Grenzen des Gehirns hinausreichen. Im Folgenden geben wir einen kurzen Überblick über die Mechanismen der Kommunikation zwischen Gehirn und Körper, wobei wir uns auf das Herz, das Immunsystem und die Darmmikrobiota konzentriert haben.

Schlüsselwörter: Gehirnblutung; Darmmikrobiota (GM); Herz; Immunsystem; ischämischer Schlaganfall.

Introduction and objectives

Worldwide, stroke is the second leading cause of death and third leading cause of death and disability combined. Ischemic stroke, which occurs when an artery supplying oxygen and nutrients to the brain is blocked, accounted for 62.4% of all incident strokes in 2019. Hemorrhagic stroke is defined by the rupture of a blood vessel. Depending on the location of bleeding, hemorrhagic stroke is further divided into intracerebral hemorrhage (ICH, 27.9%) and subarachnoid hemorrhage (SAH, 9.7% of all strokes in 2019) (GBD 2019 Stroke Collaborators, 2021).

We illustrate here that the etiology, pathophysiology, and consequences of stroke are not confined to the nervous system but extend to, among others, the heart, immune system, and gut microbiota (GM) (Figure 1). Understanding how brain–body communication leads to brain disease and is modified during the course of stroke is indispensable for the discovery of new therapeutic targets and the development of novel, more effective treatment approaches for stroke and other neurological diseases.

Brain–heart communication

The brain is exceptionally dependent on an adequate supply of oxygen and nutrients because of its high demand and inability to store energy. In healthy adults at the age of 20, the brain receives around 20% of the cardiac output at rest, a rate that decreases by 1.3% each decade (Xing et al., 2017).

The heart is innervated by sympathetic and parasympathetic nerve fibers (SNS and PNS, respectively,

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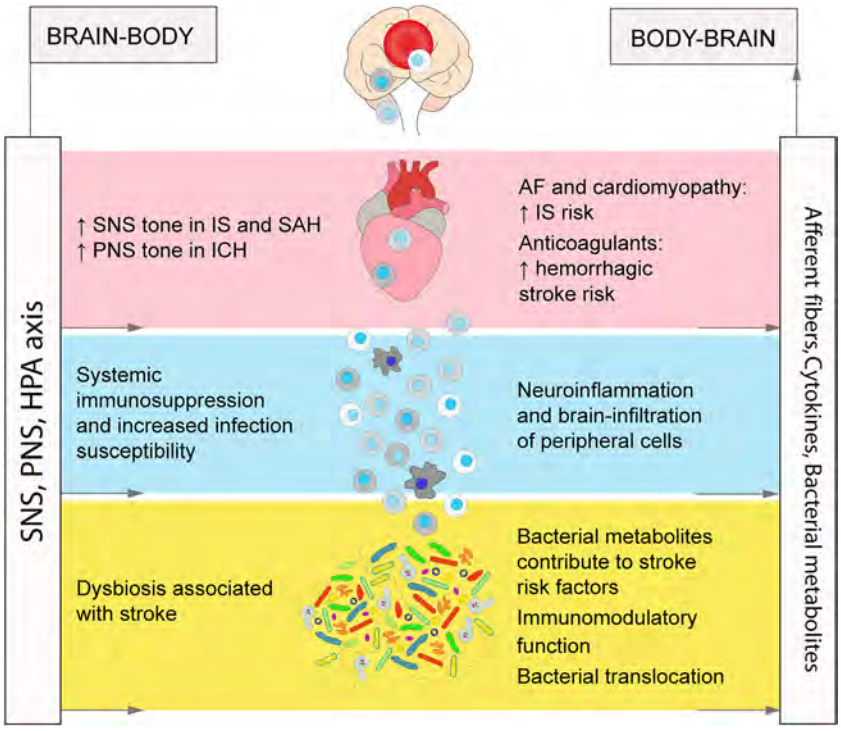

Figure 1: The three systems involved in the brain–body communication in stroke. AF, atrial fibrillation; HPA, hypothalamic–pituitary–adrenal; ICH, intracerebral hemorrhage; IS, ischemic stroke; PNS, parasympathetic nervous system; SAH, subarachnoid hemorrhage; SNS, sympathetic nervous system.

autonomic nervous system). Sympathetic innervation of the heart muscle results in the release of catecholamines from presynaptic terminals that activate postsynaptic adrenergic receptors on cardiac myocytes. This increases heart rate (chronotropy), cardiac muscle contraction (inotropy), and conduction velocity (dromotropy) and decreases heart rate variability (HRV). HRV is the variation in time interval between consecutive heartbeats. On the other hand, parasympathetic stimulation of the heart is mediated by muscarinic receptors and has opposite effects.

Heart rate and blood pressure are also regulated by the hypothalamic–pituitary–adrenal (HPA) axis that mediates the body's response to stress. Corticotropin-releasing hormone and arginine vasopressin are released from the hypothalamus leading to the liberation of adrenocorticotropic hormone from the pituitary gland. This induces the release of glucocorticoids from the adrenal cortex into the systemic circulation. Glucocorticoids then exert their effects on the heart and the vasculature via the glucocorticoid or mineralocorticoid receptor.

Cardiac dysfunction leads to stroke

Atrial fibrillation (AF) is a common arrhythmia and one of the main risk factors for embolic stroke. In the atrial endocardium, hypercoagulability, flow abnormalities, and endothelial changes must coexist to induce thrombogenesis (Goette et al., 2016). Blot clots formed in the left atrium may travel further with the flow and occlude a blood vessel in the brain. Due to its high dependence on blood supply, already a short period of supply shortage has detrimental consequences to motor, sensory, and cognitive function. AF can also lead to reduced cardiac output as well as transient cerebral hypoperfusion and hypertension involved in cognitive impairment and brain damage (Anselmino et al., 2016).

Hypertrophic cardiomyopathy causes the heart muscle to enlarge and may occur together with AF. In an observational study, patients with hypertrophic cardiomyopathy had a 1% yearly risk for embolic events including stroke, of which half of the patients were not previously documented to have AF (Haruki et al., 2016). Although the prevalence of AF in this population may vary due to ethnic/racial differences and under-recognition of AF, this indicates that hypertrophic cardiomyopathy is an independent cardiac risk factor for stroke.

Atrial cardiomyopathy has been suggested as another source for embolic stroke. It refers to abnormal atrial substrate and function, such as chamber dilation, impaired myocyte function, and fibrosis. Atrial cardiomyopathy can occur in the presence or absence of AF and may explain some of the embolic strokes without a history of AF (Ning et al., 2021). However, the molecular mechanisms of how cardiomyopathy leads to stroke remain to be elucidated.

Oral anticoagulants are commonly used to treat AF to prevent embolic stroke. However, the anticoagulant use is associated with a 7–10-fold increased risk for hemorrhagic stroke (Morotti and Goldstein, 2020). Compared to the vitamin K antagonist warfarin, direct oral anticoagulants confer a significantly lower risk in patients (Bai et al., 2017). This is in line with a preclinical study demonstrating that warfarin promoted deadly ICH in mice with induced microbleeds, whereas direct oral anticoagulants augmented the number of microbleeds without inducing long-term cognitive impairment (Pétrault et al., 2019).

Stroke leads to cardiac dysfunction

Cardiac complications, including acute coronary syndrome, heart failure, and cardiac arrhythmia, frequently occur after ischemic and hemorrhagic stroke (Chen et al., 2017; Lee et al., 2016; Scheitz et al., 2018).

Acute autonomic imbalance has been proposed as a trigger for newly occurring AF after stroke (Paquet et al., 2018). It may be induced due to damage to specific brain regions including the insular cortex that regulates the autonomic control of the heart rhythm or due to inflammatory mechanisms that result in abnormal autonomic responses. In contrast to ischemic stroke, where sympathetic predominance during the first three days and reduced HRV as a risk factor for short-term mortality and cardiac death are well-established (Yperzeele et al., 2015), a shift to parasympathetic predominance and higher HRV within the first 24 h related to the poor three month outcome has been observed in acute ICH (Rass et al., 2021; Szabo et al., 2018). This may be related to increased intracranial pressure that occurs in critically ill patients with large ICH; patients with traumatic brain injury and increased intracranial pressure were also reported to have higher HRV (Szabo et al., 2018).

Another cardiac dysfunction, commonly associated with SAH, which can also develop after ischemic stroke, is Takotsubo cardiomyopathy or Takotsubo syndrome. This syndrome presents as a transient dysfunction of the left heart ventricle and occurs in the absence of obstructive coronary artery disease. Cardiac dysfunction typically recovers spontaneously within days to weeks (Baker et al., 2021). Sympathetic overactivity due to physical or emotional stress (the latter has also led to the term “broken-heart syndrome”) results in a supraphysiological release of catecholamines that directly damages myocytes by inducing a shift from the positive inotropic to a negative inotropic response (Baker et al., 2021).

In mice, ICH induced progressive cardiac dysfunction associated with systemic and cardiac inflammation as well as oxidative stress (Li et al., 2018; Zhang et al., 2021), which were abrogated by splenectomy that also improved neurological outcome (Li et al., 2020). The authors further showed that deficiency in small ubiquitin-like modifier 1 (SUMO1) exacerbates cardiac and neurological dysfunction (Li et al., 2021).

Further, elucidating the molecular mechanisms underlying poststroke cardiac vulnerability and cardiac dysfunction leading to stroke is of major importance to identify therapeutic targets to successfully protect the heart and the brain.

Brain–immune communication

Another important player in the pathophysiology of stroke is the immune system. The brain receives constant input about inflammatory cues in peripheral tissues over visceral sensory (the vagus nerve and spinal afferents) and somatosensory nerves (spinal afferent fibers), enabling feedback and fine-tuning of immune responses (Chavan et al., 2017). Additionally, cytokines produced in the periphery may also reach the brain through the bloodstream (Meisel et al., 2005). The communication between the central nervous system (CNS) and the immune system occurs mainly over the three routes that are also involved in the brain–heart connection, i.e., the SNS, PNS, and the HPA axis (Meisel et al., 2005). Cholinergic preganglionic sympathetic fibers originating from the thoracic and lumbar parts of the spinal cord connect with postganglionic neurons secreting noradrenaline and neuropeptide Y arriving to multiple organs including blood vessels, spleen, bone marrow, and lymphoid tissue (Chavan et al., 2017). Vagal efferents starting in the dorsal motor nucleus and nucleus ambiguous provide the parasympathetic innervation of the heart and other thoracic and abdominal organs (Chavan et al., 2017).

The role of the brain–immune links after brain injury has been extensively studied in ischemic stroke. Generally, neuroimmune communication is a complex topic, and the effects in health and disease are context- and tissue-specific (Chu et al., 2020). Neuroimmune mediators can be simultaneously proinflammatory and anti-inflammatory depending on the time of exposure or type of the cellular receptor (Chavan et al., 2017).

Local and peripheral immune cells are involved in poststroke neuroinflammation

In the CNS, an abrupt drop in perfusion leads to the depolarization of neuronal cells and glia, glutamate release, and triggering of the ischemic cascade involving

excitotoxicity, peri-infarct depolarization, and cell death (Dirnagl et al., 1999). Resident phagocytes, microglia, become activated before neuronal death, upregulating proinflammatory genes. Also, astrocytes, local mast cells, and brain-resident macrophages react to the injury contributing to the neuroinflammatory response and disruption of the blood–brain barrier (BBB) facilitating the infiltration of peripheral immune cells (Iadecola et al., 2020).

Neutrophils are the first peripheral cells arriving to the brain and advancing local inflammation and BBB breakdown by secreting proteases, interleukin (IL)-1β, and neutrophil extracellular traps. Neutrophils are followed by monocyte-derived macrophages, natural killer (NK) cells, T cells activated in antigen-dependent and independent processes, and B cells (Iadecola et al., 2020). The kinetics of the immune response and the infiltration of peripheral immune cells have been relatively well-characterized in rodent models of stroke as well as human patients (Beuker et al., 2021). Notably, there are still many gaps in the detailed understanding of the impact of certain cell subpopulations and their roles for the evolution of the lesion and outcome.

Specific immune cells can have distinct (beneficial/detrimental) roles depending on the subpopulation and time after stroke (acute/chronic phase). For example, B regulatory cells are linked to favorable outcomes in experimental stroke settings due to their anti-inflammatory phenotype and ability to attract T regulatory cells to the lesion site (Seifert et al., 2018). On the other hand, B cells and plasma cells have been proposed to contribute to the development of poststroke cognitive impairment by producing antibodies against CNS antigens in the chronic phase of stroke (Doyle et al., 2015). Also, T cells secreting IL-17 (Th17 cells, γδT cells) have been linked to detrimental outcome after ischemic stroke, whereas T regs are generally associated with beneficial prognosis (Cramer et al., 2019).

CNS-resident and peripheral immune cells are also important players in the pathophysiological sequelae of hemorrhagic stroke; the detailed mechanisms are, however, less-characterized than in ischemic stroke (Shao et al., 2019).

Brain–body signaling leads to poststroke immunosuppression

Simultaneously, it is important to highlight the role of the brain–body communication axes and the fact that, after brain lesion, the immune response differs between the injured CNS and the rest of the body. In ischemic stroke, the initial systemic inflammatory boost is followed by a suppression of immune functions in the periphery (Meisel et al., 2005). It has been proposed that systemic dampening of the immune response poses, in fact, a protective mechanism to limit the infiltration of peripheral immune cells to the brain (Dirnagl et al., 2007).

Systemic immunosuppression after the insult leads, however, to increased susceptibility to infections that occur in ~30% of ischemic stroke patients. Specifically, pneumonia has been linked to increased mortality and worsening of neurological outcome (Westendorp et al., 2011). Immunosuppression mediated by the PNS (over the vagus nerve) is mostly connected to the actions of acetylcholine on macrophages upon binding to the α7 nicotinic receptor, decreasing the production of proinflammatory cytokines such as tumor necrosis factor (TNF) and IL-1 (Tracey, 2002). Stimulating the vagus nerve is known to have anti-inflammatory effects, but interestingly, as shown in experimental models, acetylcholine is not derived directly from the vagal fibers. The vagus nerve provides input to the celiac ganglion, the origin of the catecholaminergic splenic nerve. It has been therefore proposed that T cells expressing β2-adrenergic receptors are the producers of acetylcholine reaching the macrophages (Rosas-Ballina and Tracey, 2009).

Concurrently, the SNS can suppress immune function over direct actions of noradrenaline leading to a diminished production of proinflammatory cytokines in cells of the innate and adaptive immune system (Sharma and Farrar, 2020), including invariant NKT cells in the liver, where a decreased intravascular crawling of these cells and increased production of anti-inflammatory IL-10 and IL-5 were shown as effects of increased noradrenergic signaling (Wong et al., 2011). Newly identified indirect effects of SNS activation on immune cells, not explored in experimental stroke settings yet, comprise the inhibition of leukocyte migration via limiting local tissue blood flow leading to decreased leukocyte movement (Devi et al., 2021).

Finally, glucocorticoids as mediators of the HPA axis have been known for their anti-inflammatory actions, decreasing cytokine production, expression of adhesion molecules and nuclear factor kappa B (NF-κB), and induction of apoptosis in cells of innate and adaptive immunity (Cain and Cidlowski, 2017).

A further detailed characterization of regulatory mechanisms in poststroke peripheral immune responses is of great importance for both systemic complications after stroke and pathophysiological events in the CNS, since immune cells from the periphery will be recruited to the site of the lesion.

Brain–gut communication

Intriguingly, in recent years, the GM (microbial community inhabiting the intestines) has been identified as a potential immunomodulator in health and disease, including stroke (Cryan et al., 2020). Besides other functions, gut bacteria influence the balance between proinflammatory IL-17-producing T cells and T regs, which plays an important role in the pathophysiology of ischemic stroke, as already discussed above (Benakis et al., 2016; Singh et al., 2016).

But, how is it possible that what happens at the gut microbiota level reverberates on the CNS? One of the first things we need to understand to answer this question is that there is a bidirectional communication between the brain and the gut. Both neuronal and nonneuronal communication pathways are involved in this crosstalk. For brain → gut signaling, the gut wall receives direct and indirect communication from the PNS, SNS, and the enteric nervous system, which together influence microbiota makeup, resident immune cell activation, gut motility, and permeability. Moreover, the HPA axis also represents an important input to the gut in response to stress. For gut → brain signaling, afferent fibers of the vagus nerve can be stimulated by microbial molecules and enteroendocrine hormones released in the gut epithelial layer (e.g., serotonin and glucagon-like peptide-1) that influence hypothalamic neurons and the activity of the pituitary gland. Bacterial cellular components, such as lipopolysaccharide (LPS), have been shown to induce neuroinflammation, whereas GM metabolites such as neurotransmitters, indoles, bile acids, and short-chain fatty acids (SCFAs; acetate, propionate, and butyrate) are able to travel to the brain through blood and modulate the function of glia, neurons, and the BBB (Durgan et al., 2019).

Stroke is associated with gut dysbiosis

Gut dysbiosis refers to a detrimental imbalance in bacterial composition, metabolic activity, and distribution in the gut. It can result from (1) a diminished representation of beneficial bacteria, (2) overgrowth of "pathobionts" – potentially pathogenic bacteria, and (3) decreased bacterial diversity (DeGruttola et al., 2016).

Gut dysbiosis has been linked to several risk factors for stroke such as hypertension, diabetes, atherosclerosis, aging, vascular dysfunction, and obesity (Durgan et al., 2019) and was reported after stroke (Holmes et al., 2020; Lee et al., 2021). It has the potential to impact ischemic stroke outcome, e.g., through the fine-tuning of the immune response (Benakis et al., 2016; Singh et al., 2016). Additionally, other mechanisms such as increased intestinal permeability and potential bacterial translocation have been proposed as modulators of stroke prognosis (Durgan et al., 2019).

Clinical cohort studies suggested that ischemic stroke triggers dysbiosis due to the overgrowth of pathogenic bacteria that reciprocally exacerbates brain damage (Xu et al., 2021). In another study in patients exhibiting three or more risk factors for stroke without prior history of stroke, opportunistic pathogenic bacteria were reported to be enriched, whereas beneficial bacteria were depleted (Zeng et al., 2019). Hypertensive patients also demonstrated reduced levels of beneficial bacteria, whereas the levels of pathogenic bacteria were increased (Avery et al., 2021). Rodent models of hypertension generally replicate these findings. However, data are still controversial when it comes to the ideal microbial makeup, especially concerning some phyla (i.e., Bacteroidetes) (Marques et al., 2017).

Despite some insight into gut dysbiosis in ischemic stroke, little is known about hemorrhagic stroke. In a mouse model of ICH, alterations of microbial diversity and gut dysbiosis were related to reduced intestinal motility and increased gut permeability. Interestingly, recolonizing ICH mice with healthy microbiota ameliorated neuroinflammation and functional deficits after ICH (Yu et al., 2021).

Microbial metabolites modulate stroke risk and outcome

GM metabolizes phosphatidylcholine from dietary sources (e.g., eggs and red meat), leading to the formation of trimethylamine and finally trimethylamine N-oxide (TMAO), which was associated with an increased risk of major adverse cardiovascular events, carotid artery stenting, and first stroke (Lee et al., 2021). A recent systematic review proposed that inflammation and aging simultaneously contribute to changes in GM composition, and ischemic stroke predisposition was linked to significantly higher TMAO levels and a reduction of SCFA-producing bacteria (Lee et al., 2021). In addition, other GM-derived metabolites such as phenylacetylglutamine enhanced thrombosis risk through the activation of adrenergic receptors in platelets (Nemet et al., 2020).

SCFAs are one of the main bioactive microbial metabolites that constitute major products from bacterial fermentation of dietary fiber in the intestine (mainly acetate, propionate, and butyrate), favoring usually beneficial actions in the host. Propionate showed cardioprotective effects through attenuating systemic inflammation and abrogating

cardiac hypertrophy, fibrosis, vascular dysfunction, and hypertension (Bartolomaeus et al., 2019). GM modulation and acetate supplementation protected against obstructive sleep apnea-induced gut inflammation and hypertension and mitigated blood pressure increases, cardiac fibrosis, and left ventricular hypertrophy (Marques et al., 2017).

In acute ischemic stroke patients, SCFA levels were inversely correlated with stroke severity and prognosis, suggesting SCFAs as potential prognostic markers and therapeutic targets (Tan et al., 2021). In aged mice subjected to ischemic stroke, fecal transplantation of SCFA producers attenuated inflammation and neurological deficits, increasing the concentration of SCFAs in the gut, plasma, and brain (Lee et al., 2020). Moreover, acetate, propionate, and butyrate supplementation in drinking water before induction of stroke in the photothrombotic mouse model facilitated lymphocyte recruitment to the infarcted area, resulting in microglial activation and neuronal plasticity as well as improved limb motor function recovery (Sadler et al., 2020). Among the most abundant SCFAs, levels of butyrate were most strongly negatively correlated with neurological outcome and infarct size in a rat model of ischemic stroke. Its supplementation effectively remodeled GM and repaired the leaky gut, not to mention that transplanting SCFA-enriched fecal microbiota also reduced neurological deficits, brain edema, and infarct sizes (Chen et al., 2019).

The described roles of gut commensals and their connection to the brain function offer a new and exciting area of research potentially providing more options in search for therapeutic targets (Durgan et al., 2019).

Is it possible to therapeutically target the brain through the periphery?

Considering the fact that neuroprotective strategies have not been successful in clinical trials, new therapies targeting the brain–body communication after stroke and poststroke complications may help improve the outcome after CNS lesion.

Protecting the brain is protecting the heart

Tremendous effort has helped to improve anticoagulants for the treatment of AF and to reduce the risk of brain hemorrhage. When it comes to poststroke cardiac dysfunction, alleviating autonomic imbalance will be key to protect the heart. This may be achieved by decreasing sympathetic overactivation inhibiting beta-adrenergic receptors or the renin–angiotensin–aldosterone system. However, pharmacological treatments remain insufficient. Recently, cardiac neuromodulation of various types to restore sympathovagal balance has emerged. Preclinical studies have shown promising results of bioelectric therapies for cardiac diseases, but more clinical studies are needed to identify optimal stimulation parameters and location (Hanna et al., 2018). Whereas neuromodulation of the brain is currently investigated for poststroke motor recovery, its effect on the heart is an outstanding area of research. An alternative approach is to improve heart function and ameliorate autonomic dysfunction of the heart by exercise (Katz-Leurer and Shochina, 2007). Thus, clinical trials on neurorehabilitation should focus on identifying the most beneficial exercise regime that also targets heart health.

Fine-tuning the immune response to impact the poststroke outcome

Most drugs already tested in clinical trials and directed against the poststroke neuroinflammatory response interfered with the entry of peripheral immune cells to the brain or inhibited proinflammatory signaling (Iadecola et al., 2020). When it comes to limiting poststroke pneumonia, preventive antibiotic treatment has not been established as a successful approach (Meisel and Smith, 2015). Also, more studies would be necessary in the field of immunostimulatory therapies to boost peripheral immune responses or block stroke-induced immunosuppression (Faura et al., 2021). Selected agents (beta blockers) modulating the poststroke brain–body signaling have also been tested in clinical studies; however, current data do not show significant benefits in acute ischemic stroke (Balla et al., 2021). Therefore, more research on neuroimmune interactions after stroke is urgently needed to pinpoint potential therapeutic targets.

You are what you eat!

There are several options to target the gut–brain axis and the GM for therapy in stroke: (1) Fecal microbiota transplantation, whereby the microbiota of a healthy donor is transferred to a patient, can be used to increase microbial diversity and the percentage of beneficial microbiota in the gut. Fecal microbiota transplants are currently

investigated in a clinical trial for Alzheimer disease and have been successful in preclinical models of stroke (Holmes et al., 2020). (2) Probiotics (live and beneficial bacteria) and prebiotics (nondigestible dietary substances to foster the growth of favorable microorganisms) have been demonstrated to decrease gut inflammation as well as improve cognitive performance in middle-aged and older adults with cognitive impairment (Sanborn et al., 2020). Data on the beneficial effects of probiotics and prebiotics are currently limited to preclinical studies; however, a clinical trial evaluating probiotics for ischemic stroke patients is under way (Holmes et al., 2020). (3) Dietary interventions aim to foster the growth of beneficial bacteria already present in the gut. Whereas certain diets are known to promote healthy aging including cognitive function and have been shown to have significant effects on microbial diversity (Holmes et al., 2020), data on stroke are limited. Overall, further clinical trials are needed to assess the benefit of targeting the GM and gut–brain signaling for stroke therapy.

An ounce of prevention is worth a pound of cure

Whereas most therapeutic targets are developed to ameliorate poststroke outcomes, we also need to better understand how cardiac dysfunction, immune imbalance, and gut dysbiosis lead to CNS vulnerability to stroke. Hence, model systems addressing body–brain communication imbalances should be developed to study these axes and to develop further preventative treatments.

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Review article

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Epigenetic function in neurodevelopment and cognitive impairment

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Abstract: Brain development comprises a fine-tuned ensemble of molecular processes that need to be orchestrated in a very coordinated way throughout time and space. A wide array of epigenetic mechanisms, ranging from DNA methylation and histone modifications to non-coding RNAs, have been identified for their major role in guiding developmental processes such as progenitor proliferation, neuronal migration, and differentiation through precise regulation of gene expression programs. The importance of epigenetic processes during development is reflected by the high prevalence of neurodevelopmental diseases which are caused by a lack or mutation of genes encoding for transcription factors and other epigenetic regulators. Most of these factors process central functions for proper brain development, and respective mutations lead to severe cognitive defects. A better understanding of epigenetic programs during development might open new routes toward better treatment options for related diseases.

Keywords: monogenic disease; neural development; transcriptional regulation.

Zusammenfassung: Die Gehirnentwicklung basiert auf zeitlich und räumlich fein aufeinander abgestimmten Entwicklungsprozessen, wie Proliferation neuronaler Vorläuferzellen, deren Migration und Differenzierung. Die diesen Vorgängen zu Grunde liegenden Genexpressionsprogramme werden durch epigenetische Mechanismen wie DNA-Methylierung, Histonmodifikationen und nicht-kodierenden RNAs gesteuert und moduliert. Diverse Neuroentwicklungskrankheiten beruhen auf dem Verlust oder der Mutation von Genen, die für epigenetische Regulatoren kodieren, wodurch die Relevanz epigenetischer Transkriptionskontrolle für die Gehirnentwicklung verdeutlicht wird. Viele dieser Faktoren regulieren kritische Aspekte der neuronalen Entwicklung, was erklärt, warum entsprechende Mutationen zu schwerwiegenden kognitiven Defiziten führen können. Daher kann ein besseres Verständnis von epigenetischen Regulationsnetzwerken neuronaler Entwicklungsprozesse neue Wege zur Etablierung von verbesserten Therapiestrategien für assoziierte Erkrankungen eröffnen.

Schlüsselwörter: monogene Krankheiten; neurale Entwicklung; Transkriptionsregulierung.

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Cognitive deficits in neuropsychiatric and neurological disease

For an entire range of neuropsychiatric diseases, cognitive deficits are among the core symptoms of impaired function. This is the case for schizophrenia that is characterized by disorganized thinking and severe working memory deficits. Patients with autism tend to have a reduced IQ along with delayed cognitive development and often display strong perseverations in working memory tests (Sotoodeh and Taheri-Torbati, 2021). Also, major depressive disorder (MDD) can be accompanied by a variety of cognitive changes (depending on the subtype and severity of the disease manifestation). These defects range from working memory deficits and the ability to focus on intellectual assignments to long-term memory impairment and disturbed mode of thinking (rumination), caused by reduced control of higher brain regions on the thought process (Yang et al., 2021). Currently, it is still under debate if and how genetic factors contribute to the development of MDD (e.g., Wray et al., 2018) and whether those give rise to a subtle altered brain morphology which renders the brain vulnerable to disease later on. Another line of research investigates early life stress (ELS) as a factor which may

leave an organism more vulnerable to MDD as well (Zhang et al., 2021). Herein, ELS is believed to interfere with brain development, either by affecting molecular pathways through epigenetic processes or through a direct effect of stress hormones on the developing brain. This translates into interference with the transcriptional machinery required for proper wiring of neural cells, including different neuronal subpopulations (excitatory vs inhibitory), their density, and distribution (Albrecht et al., 2020; Zhang et al., 2021). By contrast, schizophrenia and autism are thought to be clearly caused by developmental perturbations or at least have a strong developmental component. Regarding schizophrenia, which is a multifactorial and multigenic disease, it is believed that its genesis requires, according to the "*two-hit-hypothesis*", two insults. Herein, one insult, which could be a genetic predisposition or an environmental event (first hit), affects the organism during an early vulnerable phase of brain development, leaving a morphological, physiological, or molecular "scar" in the brain (Maynard et al., 2001). A brain primed this way will be vulnerable to other insults later in life, including severe stress (second hit). This theory may as well apply to the development of MDD.

One specific group of neuropsychiatric diseases, leading to cognitive defects through its impact from early developmental stages, are monogenic diseases. This observation is even more relevant for neurological diseases. Due to the developmental aspect in the etiology of those diseases, they also belong to the group of neurodevelopmental disorders (NDDs), which also include other neurological diseases such as epilepsy. Interestingly, among the genes being causative for monogenic disease, a large number of genes can be identified which encode for enzymes involved in the regulation of epigenetic function (reviewed in Jakovcevski and Akbarian, 2012). This review aims to describe the understanding of how the human cerebral cortex is developed, which might hold great promise to diagnose and treat NDDs (Reichard and Zimmer-Bensch, 2021). Specifically, we will refer to the involvement of epigenetic mechanisms as transcriptional regulators of regular development, being sensitive and vulnerable to genetic and environmental as well as internal and external clues. After describing the neurodevelopmental principles of proper neural wiring and migration, we will review important players of the developmental transcriptional machinery. Then, we will elaborate on the impact of diverse epigenetic mechanisms (DNA methylation, the action of lncRNA, and histone modifications) on certain aspects of neurodevelopment, including cortical progenitor proliferation and differentiation (neurogenesis), the switch from neurogenesis to gliogenesis and cortical neuron migration, and maturation and survival. Whenever applicable, we link those findings to NDDs.

Developmental principles of the neocortex

A central region in the mammalian brain and the seat of higher cognitive functions is the cerebral cortex, being composed of the six-layered neocortex and the allocortex, which includes the hippocampus. The cerebral cortex controls complex cognitive behaviors by its highly specific and sophisticated neuronal networks (Geschwind and Rakic, 2013). Its proper functionality critically depends on the correct formation during embryonic and postnatal development, requiring precise interplay of distinct developmental processes, such as progenitor proliferation and differentiation into neurons and glia cells, cellular migration, morphological maturation, and the establishment of synaptic contacts. Moreover, programmed cell death represents an integral process shaping the final number of neurons and proper neuronal circuits (Southwell et al., 2012; Subramanian et al., 2019). In the cerebral cortex, these circuits are established by two major types of cortical neurons: excitatory principal neurons that express glutamate as transmitter and inhibitory γ-aminobutyric acid (GABA)-expressing local interneurons, which make up the minority (25–30% in humans and 15–20% in mouse) of the entire neuronal population of the cerebral cortex (Geschwind and Rakic, 2013).

The human cortex is generated during the first two trimesters of gestation, whereby the excitatory principal neurons and inhibitory interneurons derive from distinct proliferative niches (Subramanian et al., 2019). The population of excitatory principal neurons (70–85% of neuronal cells in the cortex) originates from progenitors located in the proliferation zone of the dorsal telencephalon. Upon becoming postmitotic, immature neurons migrate along the basal processes of the radial glia cells (RGCs), the apical progenitors residing with their soma in the ventricular zone (VZ), toward the pial surface, forming the cortical layers within the cortical plate (CP) as a transient developmental structure (Shibata et al., 2015; Zimmer-Bensch, 2019).

The highly diverse group of inhibitory GABA-expressing interneurons are generated in particular domains of the basal telencephalon (Subramanian et al., 2019; Zimmer-Bensch, 2018). These include the medial ganglionic eminence (MGE), which gives rise to parvalbumin (PV)-positive basket and chandelier cells, and somatostatin

(SST)-expressing Martinotti and multipolar interneurons. Moreover, different interneuron subtypes, such as neuropeptide Y (NPY)-, reelin-, PV-, SST, and CTIP2 (also known as BAF chromatin remodeling complex subunit, BCL11B)-expressing interneurons are derived from the preoptic area (POA). Additionally, the caudal ganglionic eminence generates reelin-expressing interneurons, vasointestinal peptide (VIP)-/calretinin-positive bipolar cells, and VIP-/cholecystokinin-expressing basket cells (Gelman and Marín, 2010; Gelman et al., 2009; Zimmer-Bensch, 2018). After invading the cerebral cortex through the intermediate zone/SVZ and the marginal zone (MZ) (Guo and Anton, 2014; Tanaka and Nakajima, 2012), interneurons spread tangentially across different cortical areas before they switch from the tangential to the radial mode of migration to reach their cortical target layers (Hatanaka et al., 2016).

Correct numbers of excitatory principal neuron and inhibitory interneuron subtypes have to be generated and connected to guarantee proper cortical function. Of note, malfunction of PV+ interneurons (Nakazawa et al., 2012) and diminished expression of reelin (Ishii et al., 2016) have been reported as causatives for the cognitive deficits in schizophrenia.

Transcriptional programs during neural development

Of intrigue, complex transcriptional networks control and direct all these developmental steps of cortical neuron generation, migration, and maturation that have been described in excellent reviews to which we refer for more detailed insights (Shibata et al., 2015; Ypsilanti and Rubenstein, 2016; Zimmer-Bensch, 2018). An example for a transcriptional cascade governing the fate-specification and proper development of MGE-derived cortical interneurons will be exemplarily discussed as follows. The transcription factor NKX2.1 (NK2 homeobox 1) is expressed by progenitor cells of the MGE, giving rise to PV+ and SST+ cortical interneurons as well as to neurons fated for the striatum. In contrast to striatal-fated neurons, NKX2.1 is downregulated in postmitotic interneurons destined for the cerebral cortex, whereas LHX6 (LIM homeobox protein Lhx6), SOX6 (transcription factor SOX-6), and SIP1 (Smad interacting protein 1) are expressed at postmitotic stages, and SATB2 (SATB homeobox 2) expression is triggered in these migrating MGE cells upon invasion in to the cortex. NKX2.1 being at the top of this transcriptional cascade and required for the temporal specification of cortical interneuron subtypes triggers LHX6 expression (Du et al., 2008) and regulates the expression of guidance factors ensuring proper cortical interneuron migration (Nóbrega-Pereira et al., 2008). The transcription factor LIM homeobox 6 (LHX6) in turn is essential for proper development and migration of MGE-derived cortical interneurons by transcriptionally regulating migration- and maturation-related genes, such as CXCR7 (C-X-C chemokine receptor type 7), ARX (Aristaless-related homeobox) and SATB1 (SATB homeobox 1). SATB1 dictates MGE-subtype terminal differentiation and connectivity (Close et al., 2012; Denaxa et al., 2012), whereas LHX6-dependent regulation of *Arx* and *Cxcr7* expression orchestrates cortical interneuron fate and laminar position (Vogt et al., 2014). Regarding the development of autism and other disease with cognitive defects, *SATB1* (Mahjani et al., 2021) and *SATB2* (Usui et al., 2013) have both been implicated in the genesis of autism, and its downregulation is linked to impaired cognition (Jakovcevski et al., 2015).

Extrinsic factors of cell fate during development

In addition to these intrinsic programs, diverse aspects of neuronal development have been described to be influenced by "external" factors. For example, paracrine signaling of cortical progenitors, involving the membrane-bound ephrin receptors and their ephrin ligands, have been reported to control the balance of proliferation and differentiation of cortical progenitors (Gerstmann and Zimmer, 2018). Likewise, cortical interneuron development seems to rely on both intrinsic and extrinsic factors, such as diverse membrane-bound or secreted proteins and proteoglycans, that act either as chemoattractive and chemorepellent cues for migrating interneurons (Guo and Anton, 2014; Friocourt and Parnavelas, 2011; Marín et al., 2003, 2010; Zimmer et al., 2008, 2011). Mechanical forces induced by interactions of cells with their local environment, e.g., during cellular migration, being sensed by mechanoreceptors further regulate diverse aspects of brain development (Javier-Torrent et al., 2021). Interneuron positioning can further be influenced by early postnatal neuronal activity, and ambient GABA and glutamate as comprehensively discussed in diverse other reviews (Bortone and Polleux, 2009; De Marco García et al., 2011; Zimmer-Bensch, 2018). In sum, these studies emphasize the role of the local milieu or extrinsic environmental factors for proper cortical development and functionality.

Potential mechanisms mediating "gene x environment" interactions: the epigenetic interface

"Gene x environment" interactions are hypothesized to be mediated by epigenetic mechanisms that modify the readability of our genes, posttranscriptional events, and translation (for review see, Klengel and Binder, 2015). Not only environmental factors, including the local microenvironment, but also external stressors are believed to interact with the epigenetic landscape of organisms. Some of these interactions are mediated by transcription factors (Santos-Terra et al., 2021). For example, the transcription factor Nr3c1 (Nuclear Receptor Subfamily 3 Group C Member 1) is activated after stress exposure and promotes changes of the histone landscape (for review, see Deussing and Jakovcevski, 2017).

Major epigenetic mechanisms

Epigenetic mechanisms include histone variants and modifications, alterations in nucleosome positioning, DNA methylation, and noncoding RNA.

More specifically, DNA can be chemically modified by **DNA methylation**, occurring mostly on cytosines, but also on adenines in eukaryotes (Greenberg and Bourc'his, 2019). DNA methylation is catalyzed by DNA methyltransferases (DNMTs), with DNMT1 and DNMT3A being predominantly expressed in the developing and adult brain (Greenberg and Bourc'his, 2019). DNA methylation at the enhancer and promoter sites is associated with transcriptional regulation. Further, DNA methylation can occur in gene bodies and intergenic regions being involved in repression of repetitive elements, alternative splicing, and alternative promoter choice (Greenberg and Bourc'his, 2019). Despite its stable chemical nature, DNA methylation is a dynamic process even in postreplicative cells such as neurons (Lister et al., 2013; Meadows et al., 2016; Sharma et al., 2016). In contrast to passive DNA demethylation in dividing progenitors, active demethylation in neurons can be achieved by 10–11 translocation (TET) family enzyme-dependent mechanisms (Wu and Zhang, 2017; Wu et al., 2017). TETs oxidize 5-methylcytosine (5mc) to 5-hydroxymethylcytosine (5hmc) and iterative oxidation forms, which then can be actively reversed to cytosine by thymine DNA glycosylase (TDG)-mediated base excision repair (Ito et al., 2011; Kohli and Zhang, 2013; Wu and Zhang, 2017), also described in neurons (Kaas et al., 2013; Li et al., 2014).

Histone modifications include methylation and acetylation of histone proteins which lead to a chemically induced conformation change of the DNA wrapped around them, depending on the specific modification causing either a more relaxed or a condensed ensemble, and therefore the readability and ultimately gene expression capacity is regulated (reviewed in Zimmer-Bensch, 2020).

Noncoding RNAs represent regulatory RNAs that are not encoding for proteins. They can be distinguished in small and long noncoding RNAs (scnRNAs and lncRNAs, respectively), based on their size, biogenesis, and function. The miRNAs, siRNAs, and piRNAs are categorized as sncRNAs, mainly conducting posttranscriptional regulation in the cytoplasm (Matsuki et al., 2013). The lncRNAs, defined as RNA species being longer than 200 nucleotides, exhibit a broad functional repertoire, being involved in the regulation of transcription and posttranscriptional events in the nucleus and further influencing translation, e.g., by functioning as a sponge for or precursors of miRNAs (Zimmer-Bensch, 2019).

Since epigenetic mechanisms are known to concertedly modulate chromatin structure and gene expression through a diverse spectrum of interactions, this epigenetic interface is rather complex. There is extensive cross talk between DNA methylation and histone modifications, such that DNA methylation signatures can predispose for particular histone modifications and vice versa (Cedar and Bergman, 2009). DNA methylation furthermore modulates the expression of genes encoding for enzymes of histone-modifying complexes, and through this, histone modifications. Moreover, DNMTs have been reported to interact, e.g., with the polycomb-repressor complex 2 (PRC2) at protein level, thereby influencing the establishment of repressive H3K27me3 marks (Gleeson, 2001; Hiroi et al., 2011). The group of lncRNAs in turn was described to recruit or evict the binding of DNMTs and histone-modifying complexes to specific DNA loci (Barkovich et al., 2012; Matsuki et al., 2013); hence, cooperating in achieving site-specific modifications. Thus, a complex interplay between different epigenomic remodelers orchestrates transcriptional and posttranscriptional regulation. These epigenetic processes–including the interaction with the intrinsic and extrinsic environment–take place during regular development and are required for coordination of physiological functions. Perturbations of this fine tuning, either genetic or environmental, lead to morphological and functional problems during development with implications for cognitive function and disease (Reichard and Zimmer-Bensch, 2021).

Epigenetic mechanisms in neuronal development

Several lines of evidence point to crucial functions of epigenetic mechanisms in orchestrating neurodevelopmental processes. Numerous mutations of chromatin regulators have been identified to lead to defective brain development being associated with several neurodevelopmental diseases (NDDs) (Reichard and Zimmer-Bensch, 2021). Moreover, numerous transcription factors known to regulate the development of cortical neurons influence the epigenome. For example, SATB1 recruits chromatin remodeling factors to control gene transcription (Cai et al., 2006). Mutations of *SATB1* lead to a set of developmental disorders that comprise cognitive deficits and impact transcriptional activity (den Hoed et al., 2021). Alterations in histone profiles were observed in *Nkx2-1* conditional knockout animals (Sandberg et al., 2016), which were presented with learning and memory deficiencies (Magno et al., 2017), whereas the deletion of *ZEB2* (zinc finger E-box binding homeobox 2) in human embryonic stem cells affects the expression of genes associated to histone modification and chromatin organization (Stryjewska et al., 2017). Mutations in the *ZEB2* gene are the monogenic cause for the developmental disorder Mowat-Wilson Syndrome (Birkhoff et al., 2021), characterized by developmental delay and severe cognitive impairment throughout the entire life span. Moreover, several transcription factors relevant for cortical development are subject to epigenetic modifications (Albert et al., 2017), underscoring the intertwinement of the epigenetic landscape and the transcriptional networks.

Indeed, numerous studies have highlighted the importance of epigenetic information in regulating cell fate transitions, migration, neuronal survival, and maturation during cortical development, which we will discuss as follows.

Epigenetic mechanisms in regulating cortical progenitor proliferation and differentiation (neurogenesis)

The transition from expansion of NECs (neuroepithelial cells) to neuronal aRGCs during early development is characterized by extensive remodeling of repressive H3K27me3 marks (Albert et al., 2017), catalyzed by polycomb-repressor complex 2 (PRC2) with EZH2 (enhancer of zeste homolog 2) as the histone methyltransferase (Pereira et al., 2010; Figure 1). Deletion of *Ezh2* in the early-developing neocortex (E9.5) causes a loss of H3K27me3 signatures and upregulated gene expression, leading to a shift from the self-renewal cell fate of aRGCs toward differentiation (Pereira et al., 2010). Mutations in the *EZH2* gene are causal for the Weaver syndrome (Gibson et al., 2012). Patients with this syndrome suffer as well from severe intellectual disabilities. Deletion of *Ezh2* in adult mice is sufficient to impair adult neurogenesis in the hippocampus and disrupt cognitive behavior. Of note, the promoters of many transcription factors involved in the generation of bIPCs (basal intermediate progenitor cells) and neuronal differentiation, such as *Eomes* [Eomesodermin, also known as T-box brain protein 2 (Tbr2)], *Neurog1/2* (neurogenin 1/2), *Insm1* (INSM transcriptional repressor 1) and *Neurod1/2* (neurogenic differentiation factor 1) are marked by H3K27me3 during the expansion period of NPCs (Albert et al., 2017). Thus, the *Ezh2* deletion triggered loss of the repressive state of these genes could drive their premature activation. Indeed, the promoters of diverse transcription factors implicated in cell fate transitions during cortical neurogenesis display dynamic alterations of histone methylation profiles including H3K4me3, H3K27me3 and H3K79me3, proposed to mediate cell type-specific induction of gene expression (Albert et al., 2017; Büttner et al., 2010; Yang et al., 2012). Another important histone modification, which has recently been shown to be key for regulating cortical progenitor proliferation and differentiation is H3K79me2, being catalyzed by the histone methyltransferase disruptor of telomeric silencing-like 1 (DOT1L) (Franz et al., 2019) (Figure 1). H3K79me2 can have both activating and repressive functions (Franz et al., 2019). During corticogenesis, DOT1L has been reported to balance the progenitor pool and to prime upper-layer neuron identity, mainly by gene activation (Franz et al., 2019). In support of its relevance for neuronal differentiation, DOT1L was further shown to influence the differentiation of embryonic stem cells to neuronal progenitors by modulating chromatin accessibility at SOX2-marked enhancers (Ferrari et al., 2020).

LncRNAs have further been described to be involved in the regulation of NPC proliferation and differentiation (Zimmer-Bensch, 2019). As the regulation of this balance of proliferation and differentiation affects brain size, lncRNAs have been proposed as critical key players of human brain evolution (Zimmer-Bensch, 2018). For example, the lncRNA *Trincr1* (TRIM71 interacting long noncoding RNA 1) regulates the self-renewal of NPCs via acting on the extracellular signal-regulated kinases (ERK) signaling

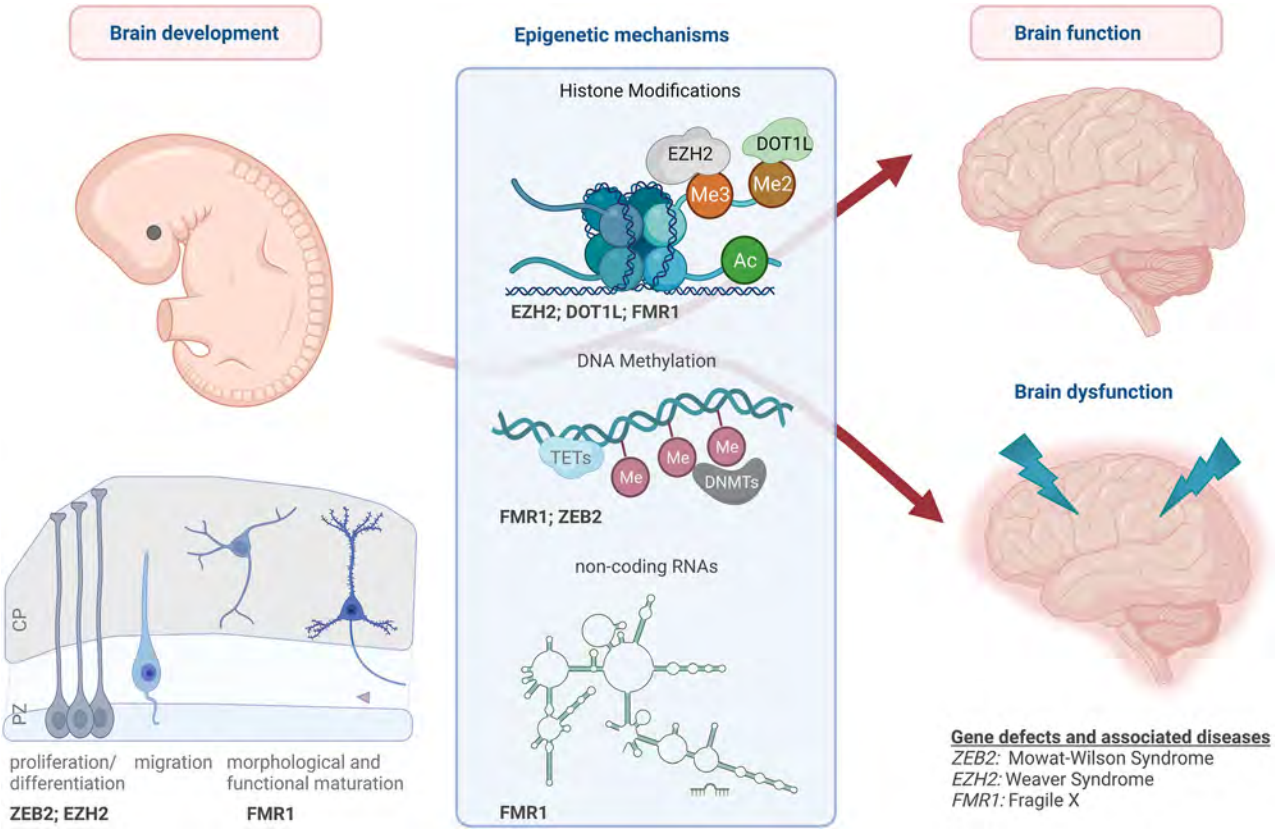

Figure 1: Disruption of epigenetic mechanisms during embryonic brain development leads to cognitive defects.
(Left panel) Schematic illustration of important aspects of neuronal development during embryogenesis, exemplarily depicted for cortical neurons. Neuronal progenitors in the proliferative zones (PZ) proliferate and differentiate, before they migrate radially to the cortical plate (CP), where they acquire morphological and functional maturation. (Middle panel) Epigenetic mechanisms, including histone modifications, DNA methylation, and the action of noncoding RNAs are critically involved in proper brain development, and (right panel) disruption of these mechanisms leads to dysfunction of the young and mature brain. Three different disease-relevant genes (*ZEB2*, zinc finger E-box binding homeobox 2; *EZH2*, enhancer of zeste homolog 2; and *FMR1*, fragile X mental retardation 1) are showcased for their impact on brain development via epigenetic mechanisms. Created with BioRender.com.

pathway, known to be crucial for progenitor self-renewal (Miyoshi et al., 2007; Valcanis and Tan, 2003). The lncRNA *Paupar* regulates the expression of genes important for neural stem cell fate such as PAX6 (paired box protein Pax-6) (Vance et al., 2014), coding for a transcription factor known to regulate progenitor cell potency, progenitor cell proliferation, and neuronal cell subtype specification (Georgala et al., 2011; Hill et al., 1991). In addition to *Pax6* transcriptional control, *Paupar* transcripts physically interact with PAX6 protein co-occupying specific genomic binding sites of PAX (Vance et al., 2014).

Other lncRNAs were reported to promote neurogenesis. The lncRNA rhabdomyosarcoma 2-associated transcript (*RMST*) physically interacts with SOX2 (SRY-box transcription factor 2), a driver of neuronal differentiation (Inamura et al., 2012; Ye et al., 2015), thereby co-regulating a large set of genes involved in neurogenesis (Schuurmans and Guillemot, 2002). Further examples of lncRNA function in regulating cortical progenitor proliferation and differentiation are presented in different reviews (Zhao et al., 2020; Zimmer-Bensch, 2019).

Apart from lncRNAs, the specification of cortical progenitors and their neuronal fate seems to further rely on posttranscriptional gene regulation by miRNAs. Numerous miRNAs exhibit unique expression profiles in the developing neocortex (Barca-Mayo and De PietriTonelli, 2014; Rajman and Schratt, 2017), and cell cycle and neurogenesis regulators have been identified among their target genes (Arcila et al., 2014).

The posttranscriptional modification of mRNAs by *N*6-methyladenosine (m6A) is an epitranscriptomic mechanism that regulates the metabolism and translation of mRNAs (reviewed in Zhao et al., 2017). Depletion of m6A in the developing neocortex affects the cell cycle length of

aRGs and shifts neuronal production to postnatal stages, which strongly proposes a role for m6A in cortical neurogenesis (Yoon et al., 2017). The transcripts found to be tagged by m6A include several transcription factors controlling NPC fate. The tagging by m6A promotes rapid turnover of these transcripts. These marks are catalyzed by the m6A methyltransferase complex with methyltransferase 14 (*Mettl14*) being an essential component. Absence of *Mettl14* induces premature expression of several neuronal lineage proteins such as NEUROD1 in aRGs (Yoon et al., 2017). *Mettl14* deletion was further reported to cause decreased radial glia proliferation and precocious differentiation (Wang et al., 2018). Interestingly, the observed phenotypes were proposed to be linked to genome-wide changes in histone methylation patterns, potentially resulting from the destabilized transcripts that encode histone-modifying enzymes. Hence, dynamic remodeling of epigenetic and epitranscriptomic signatures seems to be implicated in cortical progenitor cell fate and neurogenesis. It is important to note that m6A-tagged mRNA transcripts have been found to be enriched in synapses and largely associated with neuropsychiatric disease (Merkurjev et al., 2018), and may be relevant for regular cognitive function (Jiang et al., 2021).

The switch from neurogenesis to gliogenesis involves epigenetic mechanisms

Cortical neurogenesis is followed by a period of gliogenesis, in which astrocytes and oligodendrocytes are generated (Miller and Gauthier, 2007). The timing of the neurogenic to gliogenic transition critically determines final cortical neuron numbers and has been shown to involve epigenetic mechanisms. Histone modifications catalyzed by PcG proteins such as EZH2 modulate the expression of neurogenic and gliogenic genes, thereby controlling the onset of gliogenesis (Hirabayashi et al., 2009; Sparmann et al., 2013). The timing of astrogliogenesis was further reported to depend on DNA methylation, as conditional deletion of the maintenance DNA methyltransferase I (*Dnmt1*) in NPCs causes premature astroglial differentiation by hypomethylation of astrocyte-specific genes and genes encoding crucial components of the gliogenic Janus kinase–signal transducers and activators of transcription (JAK-STAT) pathway (Fan et al., 2005). Further, He et al. (2020) found that TET2, implicated in active DNA demethylation, promotes astrocyte differentiation from neural stem cells (NSCs) by mediating the demethylation of astroglial lineage genes including *Gfap* (glial fibrillary acidic protein). The transcription factor OLIG2 (oligodendrocyte transcription factor 2) was identified as an upstream inhibitor for *Tet2* expression, binding to the *Tet2* promoter, and thereby indirectly inhibiting astrocyte differentiation (He et al. 2020). Noncoding RNAs, such as miRNAs and lncRNAs, are also implicated in the regulation of the switch from neurogenesis to gliogenesis in NSCs in the developing central nervous system (CNS) (Mercer et al., 2010; Shimazaki and Okano, 2016).

Epigenetic regulation of the cortical neuron migration, maturation, and survival

As mentioned above, postmitotic excitatory cortical neurons conduct radial migration along the radial glia (RG) scaffold, whereas inhibitory interneurons perform tangential migration through the basal telencephalon and within the cortex before radially invading the cortical plate/layers. Different epigenetic regulators have been described to be involved in the regulation of cortical neuron migration. The chromatin remodeler BAF complex controls radial migration of cortical neurons by acting on the multipolar to bipolar transition required for proper migration, controlling gene expression programs relevant for migration (Sokpor et al., 2021).

In addition to the epigenetic state regulation of transcriptional enhancers of genes relevant for IPC generation, the histone methyltransferase PRDM16 (PR/SET domain 16) promotes cortical neuron migration through transcriptional silencing of e.g., the gene encoding the E3 ubiquitin ligase *PDZRN3* (PDZ domain containing ring finger 3) (Baizabal et al., 2018).

The migration of cortical inhibitory interneurons also underlies epigenetic regulation, involving chromatin remodeling complexes, DNMT1, histone modifications, and noncoding RNAs. The phenotypes induced by conditional removal of the RNAse III enzyme Dicer, resulting in impaired migration and differentiation accompanied by altered expression of apoptosis-related genes and genes implicated in neuronal specification, point to a critical role of miRNAs in cortical interneuron development (Tuncdemir et al., 2015).

In addition to miRNAs, cortical interneuron migration is influenced by DNMT1. *Dnmt1* deletion at postmitotic level in POA-derived cells, contributing to the pool of neuroglia form subtypes of cortical interneurons, caused morphological defects leading to an impaired migration, as well as increased rates of cell death. This resulted in diminished

numbers of NPY-expressing interneurons in the adult cortex (Pensold et al., 2017). In agreement with this, DNMT1 promotes the morphological maturation of cortical projection neurons (Hutnick et al., 2009) and dendate gyrus neurons (Noguchi et al., 2016). *Pak6* [P21 (RAC1) activated kinase 6] and *Lhx6* (LIM homeobox 6) were identified as DNMT1 target genes in POA interneurons, regulating cytoskeletal rearrangements and survival (Pensold et al., 2017; Symmank et al., 2020). Thereby, the transcriptional repression of these genes was achieved by non-canonical functions of DNMT1 interfering with the establishment of histone marks, through transcriptional control of related genes and by interactions with histone-modifying enzymes at protein level (Symmank et al., 2018, 2020).

Histone modification appears to be relevant for MGE interneuron maturation as well. For example, ARID1B (AT-rich interaction domain 1B) was reported to mediate the physical access of histone-modifying proteins to chromatin, thereby facilitating lysine 9 acetylation at histone 3 (H3K9ac) (Jung et al., 2017). This permissive histone mark appears to modulate the transcription of cortical interneuron-specific genes such as *Slc32a1* (solute carrier family 32 member 1), *Pvalb* (parvalbumin), and *Gad1* (glutamate decarboxylase 1) (Jung et al., 2017). Deletion of *Arid1b* impairs MGE interneuron survival as well as interneuron morphology, synapse structure, and inhibitory neurotransmission (Jung et al., 2017). In humans, mutations of *ARID1B* cause the Coffin-Siris syndrome (Wieczorek et al., 2013) that presents devastating developmental delay and intellectual disabilities.

Taken together, compelling evidence points to a critical role of epigenetic key players for the development of neuropsychiatric disease and severe intellectual disabilities (Ronan et al. 2013). As illustrated in this review, part of the disease genesis is likely the effect of epigenetic modifiers on mechanisms orchestrating diverse aspects of cortical development.

Since epigenetic mechanisms are reversible, they might be good targets for the development of drugs that could possibly interfere with the disease genesis from early development. This strategy would of course require early genetic testing, for at times, rare diseases that are often overlooked by GPs or even by trained pediatricians. Thus, a secondary approach should aim at treating older children, teens, and adults. Therefore, it is of high interest to determine whether those shifts in epigenetic function are maintained throughout the life span and if targeting those modifications would at least ameliorate some of the defects. Unfortunately, a full rescue of developmental disorders is not possible at later stages due to the fact that windows for morphological plasticity have been closed. The last subchapter of this review describes the relationship of epigenetic changes and cognitive abilities in the adult brain. Whenever possible, we mention findings from NDDs.

Cognition and epigenetic mechanisms in the adult brain

As for the developmental stages, epigenetic mechanisms, gene expression, and cognition are intimately intervened. For example, it has been reported that histone modifications are regulated in an experience-dependent manner, and the degree of methylation or acetylation can be induced by learning experience (Peleg et al., 2010). A pivotal role as regulators of neuroplasticity emerged for histone protein variants (Santoro and Dulac, 2015). These are additional non-allelic isoforms of the canonical histone proteins H1, H2A, H2B, H3, and H4. As for histone modifications, its initial functions have been described for developmental processes, where they form an additional regulatory layer for histone modifications and gene expression during embryonic development. A few groundbreaking studies indicate that its functions clearly reach beyond developmental plasticity. Histone variant H3.3 remains highly dynamic in the adult brain, and its turnover depends on neuronal activity as well (Maze et al., 2015). Likewise, H2A.Z is regulated and required for memory function (Maze et al., 2014). Specific links to disease with cognitive deficits have not been made, but could be an important path for future studies.

By contrast, a very clear connection has been established between histone modification and cognitive function in the adult. For example, in a mouse model of the monogenic developmental disease, Wiedemann-Steiner syndrome, conditional knockdown of the disease-relevant histone methyltransferase *Mll1* (myeloid/lymphoid or mixed-lineage leukemia1), also known as histone-lysine *N*-methyltransferase 2A (*Kmt2a*), (either via using mutant mice or by viral vector injection in the adult brain) leads to working memory deficits along with distinct changes in H3K4me3. Specifically, genes encoding for two transcription factors, namely *Satb2* and *Meis2* (MeisHomeobox 2), both linked to cognitive function and regular brain development (Gangfuß et al., 2021; Jaitner et al., 2016; Jakovcevski et al., 2015), showed reduction of H3K4me3 occupation and gene expression. Restoring levels of these transcription factors might rescue the phenotype. In the *Fmr1* (fragile X mental retardation 1) knockout mouse model for the subtype of autism, fragile-X, *Fmr1* knockout mice displayed a remarkable disrupted histone landscape

involving multiple histone marks (Korb et al., 2017) along with massive gene-expression changes. Authors identified the bromodomain-containing protein 4 (BRD4), a histone acetylation reader protein and transcription factor, as a target for alleviating some aspects of the detrimental phenotype of *Fmr1* knockout mice. Another study rescued the cognitive defects in juvenile mice by creating a double knockout with a second RNA-binding protein and restoring translational balance (Udagawa et al., 2013).

Regarding multigenic and multifactorial neuropsychiatric disease such as autism and schizophrenia, numerous studies have demonstrated changes to histone modifications and even a largely modified chromatin landscape (Jiang et al., 2017). However, in many cases, different cell types or only a subset of cell types are affected by the changes, calling for cell type-specific analysis for a clearer picture of the molecular phenotypes before therapies can be developed.

Besides refining the analysis of epigenetic signatures, future research needs to address how such epigenomic signatures respond to and integrate external stimuli to better understand and dissect the complex interplay between intrinsic programs and interactions with the local environment, which concertedly seem to act on brain development and disease pathophysiology. This will potentially promote and validate the use of occupational therapies in the treatment/alleviation of cognitive deficits.

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Bionotes

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Mira Jakovcevski is a senior scientist, currently working in the Department of Functional Epigenetics in the Animal Model (head: Prof. Dr. Geraldine Zimmer-Bensch) at the RWTH Aachen University. Prior to this position, she trained in prestigious neuroscience and neuroepigenetics labs, including the Schachner lab (ZMNH, Hamburg), Akbarian lab (UMASS Medical School, MA; Mt. Sinai, NY), and in the Neurogenetics lab at the Max Planck Institute of Psychiatry (Munich). Dr. Jakovcevski is interested in understanding the molecular aspects of how behavior and gene expression interact with each other. Herein, she focuses on epigenetic mechanisms, as an important junction between these different biological processes and a mediator of environmental factors and the genetic make up.

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Geraldine Zimmer-Bensch is a distinguished Professor of Neuroepigenetics at the RWTH Aachen University, Germany. Since the beginning of her academic career, starting at the Friedrich-Schiller University in Jena, Germany, she was fascinated by the brain and its formation. Following her postdoctoral training at the *UFRJ* in Rio de Janeiro, Brazil, she became the head of the "Neuroepigenetics" research group at the University Hospital Jena (UKJ), before being appointed as a Professor at the RWTH Aachen University. Being an independent PI at the UKJ, she focused on the identification of epigenetic regulatory networks, which direct discrete neurodevelopmental processes. Her ultimate goal is to dissect causes for neurodevelopment defects and hence, the pathophysiology of associated diseases.

Presentation of scientific institutions

Ileana L. Hanganu-Opatz* and Ilka Diester*

Forschungsgruppe (FOR5159) Resolving the prefrontal circuits of cognitive flexibility

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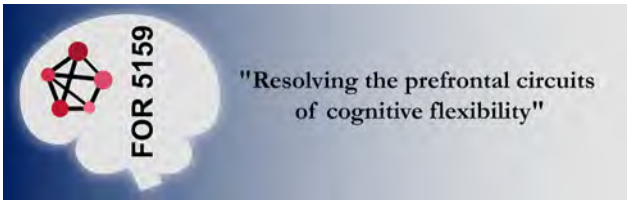

Albert Einstein once claimed that "The measure of intelligence is the ability to change". We painfully experienced the practical relevance of this fact during the last pandemic years, when we suddenly had to change our time management, implement new ways of interactions and reevaluate the importance of previously barely relevant items, e.g., face masks, test kits, and disinfectants, to name just a few examples. Our successful survival in a permanently changing environment would not be possible without the ability to store and update new evidence, (re)-evaluate the choices and take adaptive decisions. This amazing ability to easily change according to the situation defines the cognitive flexibility of our minds. It implies that low-level sensory and motor processes are internally coordinated to endow the brain with the capacity to develop and adapt internal goals and act accordingly. It is obvious that such processes involve a neural circuitry that extends over much of the brain, yet it is commonly held that the prefrontal cortex (PFC) is a critical hub (Chini and Hanganu-Opatz, 2021; Miller and Cohen, 2001). Despite the relevance of cognitive flexibility for day-to-day life, a mechanistic understanding of prefrontal coding of behavioral flexibility is still lacking, mainly due to the ethical concerns and technical limitations of human research, on the one hand, and the absence of a translational consensus regarding the prefrontal region, on the other hand (Carlen, 2017).

To fill this knowledge gap, the German Research Foundation (DFG) funds a new Research Unit FOR5159 "Resolving the prefrontal circuits of cognitive flexibility" with 4.1 million Euro for four years. FOR 5159 is a consortium integrating the universities Hamburg, Freiburg, Tübingen, Munich, Frankfurt, Mannheim, and Vienna and complements local initiatives, strengthening the Neuroscience research at national level. The FOR5159 aims to elucidate the mechanisms that enable neuronal populations in PFC to code for cognitive flexibility. For addressing this, the novel technical developments of recent years, which enable targeting, monitoring, and manipulating individual neurons and neuronal populations, are combined with data-constrained computational models that offer an integrative view embedding species-relevant similarities and differences. To enable in-depth investigations and comparisons between species, the focus of the FOR5159 will be laid on two complementary processes within the large spectrum of cognitive flexibility: working memory (WM, i.e., the short-term memory for quick access) and decision making (DM, i.e., the ability to act according to an anticipated outcome). Investigating mice, rats, primates, and humans, the consortium tests the hypothesis, that cognitive flexibility relies on temporally coordinated prefrontal ensembles defined by their outputs and inputs (see Figure 1).

A major aim of the consortium is to elucidate how temporal coordination enables the binding of neuronal populations in PFC in a task-dependent manner. The following key questions will be addressed: (i) Which patterns of neuronal firing in PFC do code for the same task component across species and which ones are common across tasks in one species? (ii) Which neuronal subtypes are activated during specific tasks? (iii) How are different types of neurons interconnected across and within cortical layers to build functional microcircuits in a task-dependent manner or across tasks? (iv) Do these neurons causally control behavioral performance? (v) How does frequency-specific oscillatory synchrony temporally coordinate the

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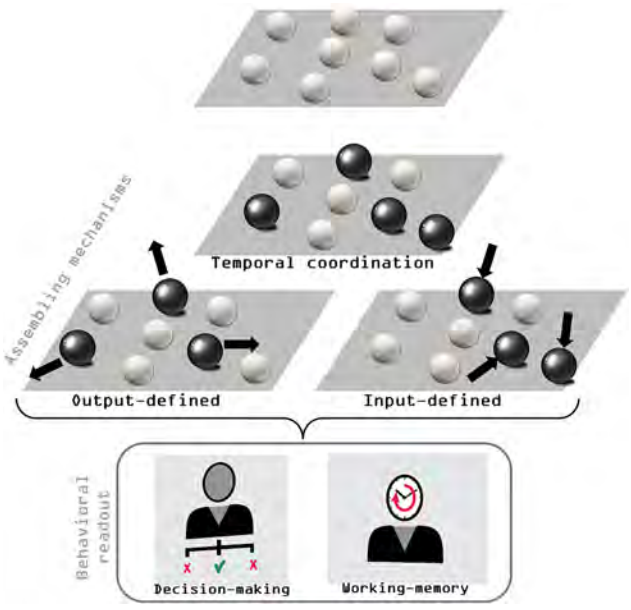

Figure 1: Proposed prefrontal mechanisms of cognitive flexibility. Depending on the context, prefrontal neurons build temporally coordinated ensembles defined by outputs or inputs that account for behavioral performance (WM and DM).

firing of neuronal populations during a specific task? To address these questions, the task-related activity patterns of identified individual prefrontal neurons during WM (TP1, TP3, TP4, TP5, TP7) and DM (TP1, TP2, TP3, TP4, TP5, TP6) will be assessed. In rodents, the identified task-related neuronal populations will be manipulated and their contribution to behavioral performance during distinct phases of the task will be monitored. A particular strong point of the consortium is the ability to monitor these patterns during the same task across species and developmental stages as well as across tasks in the same subject. For example, coordinated firing and network activity during different phases of WM or DM tasks will be recorded in the PFC of rats (TP2, TP6) and mice (TP1, TP3, TP7) as well as monkeys (TP4) and humans (TP5). This approach will enable us to identify computations within prefrontal microcircuits common across species. TP9 will test whether these computations strongly depend on the network state prior to the task.

TP7 will elucidate to which extent the prefrontal ensembles dynamically coding for working memory overlap with those dedicated to stable representations. Moreover, TP1 will identify the developmental time windows of critical relevance for the emergence of task-related prefrontal ensembles. Recordings from the same prefrontal neurons during multiple tasks in mice (TP3) and humans (TP5) will be performed to examine to what extent independent or overlapping neuronal populations in PFC are flexibly recruited. Using recurrent neural network (RNN) models inferred directly from physiological and behavioral data by deep learning methods, the features of task-related prefrontal activation and processing will be integrated across cell types, layers, ages, and species (TP8).

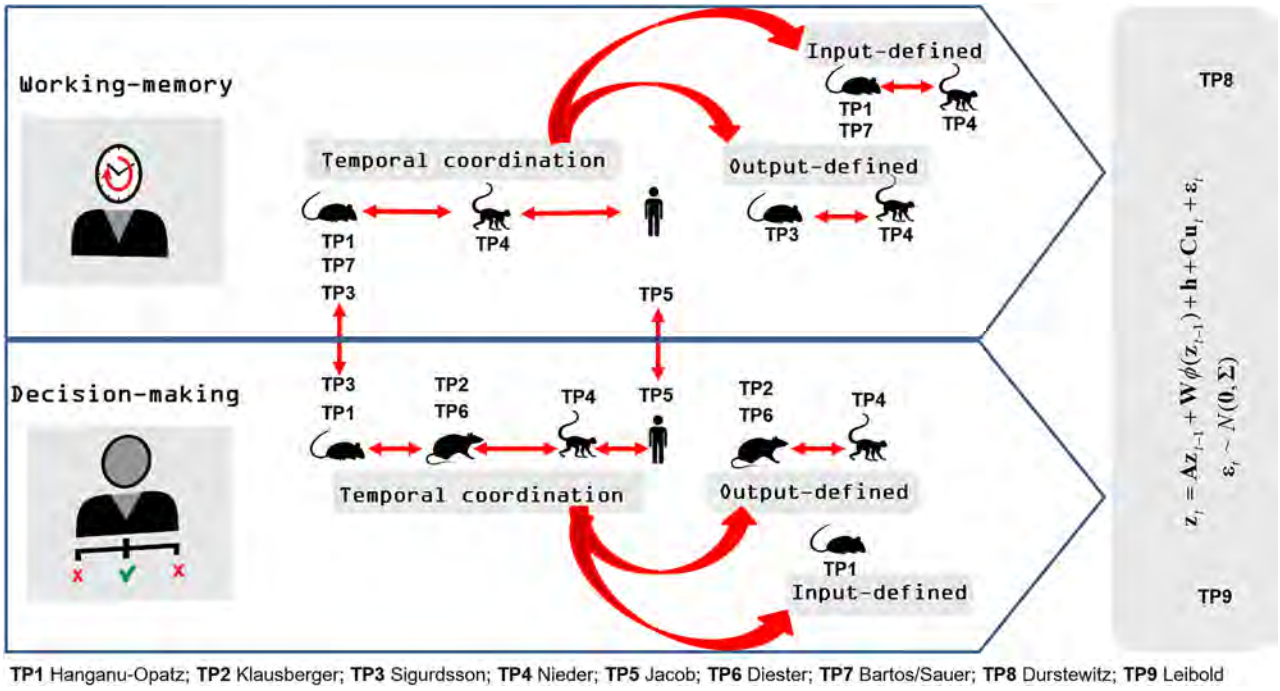

Figure 2: Schematic diagram of the research program. The interactions between the projects addressing the main hypotheses in different species (mouse, rat, primate, human) are schematically displayed for and across behavioral tasks. The resulting data will be integrated into models to extract the general rules of ensemble formation.

A second major aim of the consortium is to uncover how the projection-defined organization of PFC controls the formation of functional ensembles in WM and DM. Using recently developed tools for targeting projection-defined neuronal subpopulations, the prefrontal ensembles organized through communication with thalamic nuclei (TP6), ventral tegmental area (TP3), as well as parietal and premotor areas (TP4) will be investigated (see Figure 2).

The implementation of all these data into computational models (TP8) might uncover fundamental principles of how the PFC interacts with other brain areas to implement flexibility-related computations.

Finally, the FOR5159 will assess the role of hippocampal and thalamic inputs for the development (TP1) and function (TP7) of neuronal ensembles during WM and DM in relationship with the network state prior to the task (TP9).

The FOR5159 will provide comprehensive knowledge about the mechanisms of prefrontal processing underlying aspects of cognitive flexibility through life in mammalian species. Using cutting-edge technologies of recent years and truly translational approaches (i.e., same experimental paradigms in rodents, non-human primates, and humans integrated within a modeling framework), we will identify species-independent strategies that rest on dynamic formation of neuronal ensembles coding for a specific behavior as well as specializations accounting for species-characteristic complexity of cognitive demands. In the long run, achieving these goals is the pre-requisite for understanding the mechanisms of disease-related loss of cognitive flexibility. For neuropsychiatric disorders, such as schizophrenia and autism, it represents one of the major burdens with dramatic consequences for the daily life.

The FOR5159 will be launched in January 2022. The topic and research of the consortium will be highlighted in a symposium at the FENS 2022 in Paris.

Homepage FOR5159 (to be launched by end of January 2022): www.FOR5159.de.

Author contributions: All the authors have written the manuscript, have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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Nachrichten aus der Gesellschaft

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NeuroCon2021 - Bespoke conference for early-career brains

The Young German Neuroscience Society (jNWG) takes a stand to support the next generation of neuroscientists. To this end, the jNWG had its first, fully self-organised early-career neuroscientific meeting, the *NeuroCon 2021 – Science*$^{+}$, from November 5th–7th.

The meeting was held at Schloss Reisensburg, the conference castle of Ulm University beautifully located at Danube river, and featured a host of novel activities specifically tailored for early-career neuroscientists:

Students and doctoral as well as postdoctoral early-career researchers (ECRs) were enabled to (1) build their own network, (2) present and discuss their science in an unsupervised, peer-to-peer setting, and (3) facilitate their career by skill building. 43 Early-career scientists and five guests from 17 different cities joined the meeting, making it a great event for expanding the participants' network beyond their individual, institutional scope. Furthermore, thanks to the generosity of various supporters, free accommodation and catering at Schloss Reisensburg were provided to the participants, thereby enabling the participation of ECRs from diverse backgrounds and at all career stages.

The NeuroCon 2021 offered an intense 2-day program split between science-related activities and skill-building sessions, coupled with plenty of opportunities for personal exchange between the attendees.

Scientific activities

The NeuroCon was kicked-off by Dr. Albert C. Ludolph, former president of the German Neuroscience Society, alluding to the Reisensburg as "*the birthplace of various successful and ongoing initiatives* […]. *It is perhaps auspicious that the first meeting of the jNWG* (*NeuroCon*) *is held at this eminent venue*". Afterwards, Dr. Sanja Bauer Mikulovic (group leader at the Leibniz Institute for Neurobiology, Magdeburg) took it away in a first plenary lecture on neural network interaction in cognition, locomotion, and emotion. Besides introducing ECRs to her research (Mikulovic et al., 2018; Mocellin and Mikulovic, 2021), she shared valuable anecdotes on twisted career paths and the unpredictability in career planning. The second invited speaker, Dr. Rainer Schwarting (Director of the department of behavioral neuroscience at the University of Marburg), shared

fascinating findings and the current understanding from one of his long-standing interests: rodents' ultrasonic vocalizations and their general usefulness in neurobehavioral research (Markus Wöhr and Schwarting, 2013).

Furthermore, during the 2-day NeuroCon program, most participants took the chance to present their work during two oral sessions and/or two poster sessions. Nine talks and 25 posters from different fields of neuroscience were presented and vividly discussed, as the schedule featured plenty of time for low-pressure, peer-to-peer scientific discussions and personal feedback. In a voting, the attendees voted for the best poster and best talks of the NeuroCon meeting. Lena Erlebach, a PhD student from the Hertie Institute for Clinical Brain Research (Tübingen), received the best talk-award for her presentation on "A human(ized) system to study microglial biology ex vivo". Master student Carolin Koreny from the University of Wuerzburg won the voting for the best poster-award with her work elucidating the "Generation of human-induced pluripotent stem cell lines (hiPSC) from healthy controls and ADHD patients".

"I was more than happy […] to present a poster at a scientific conference for the first time, although I am still a master student. But NeuroCon was created for this very reason: To give space to early career researchers. The whole experience was topped off with the "Best Poster Award", which was a great honor as I was together with many great PhD students and post-docs." – Carolin Koreny

"The NeuroCon-Science+ was a great first in-person conference for me! The meeting allowed me to present my project to a broader audience for the first time and I really enjoyed the discussions […]. The NeuroCon allowed me to connect with other neuroscience PhD students and early postdocs in a very nice atmosphere, without pressure […], and opened the door for new collaborations."
– Lena Erlebach

Skill building and exchange

In addition to scientific exchange, the NeuroCon-concept strongly focused on skill development and networking aspects. Therefore, one entire afternoon was dedicated to comprehensive, expert-led hands-on workshops: Dr. Tracey Weissgerber, a meta-science expert from the Berlin Institute of Health (Charité Berlin; @T_Weissgerber), shared her expertise on dos and don'ts in "Data Visualization" (Weissgerber et al., 2015, 2019). After sensitising participants to common errors and misconceptions in scientific visualization, they were given at hand tools to improve their own data presentation skills. Simultaneously, the science journalist and writer Dr. Bradley van Paridon (@bvanparidon) taught his workshop participants how to excel in "Science communication" to share their science with a broader audience. In the evenings, participants furthermore could join "Crackle Corners": Brief, peer-to-peer introductions and subsequent small group exchange covering the following topics: scientific literature management, digital lab books, science communication in social media, as well as time- and self-management. The Crackle Corners were moderated by NeuroCon organizers and evoked very fruitful discussions and exchange. Furthermore, all workshop- and Crackle Corner-related material was shared with all participants via the jNWG Slack channel to maximise participants' benefits.

The NeuroCon – successful concept for future meetings

The NeuroCon was received and evaluated very well by the participant. The organisers would like to cordially thank the following generous supporters that made the first NeuroCon meeting possible: Gemeinnützige Hertie-Stiftung, Avisoft Bioacoustics, NWG, Chroma Technology Corporation, AHF Analysentechnik AG, Hello Bio Ltd, Hölzel Diagnostika Handels GmbH, The Jackson Immunoresearch Laboratories Inc., Miltenyi Biotech, and Thor Labs Inc.

The jNWG is part of the German Neuroscience Society (Neurowissenschaftliche Gesellschaft, NWG) and the platform to facilitate career development and communication among early-career neuroscientists within Germany and beyond. Additionally, jNWG's mission is to increase early-career scientists' visibility and to represent their needs within the neuroscience landscape. Therefore, the jNWG organizes various forms of events and is very much looking forward to involving more young neuroscientists in its mission. Also, planning for the next NeuroCon in 2022 has just started!

Want to know more? Then visit https://jnwg.org/, e.g., via the QR-Code, and register for updates at jnwg@nwg-info.de.

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NEU auf dasGehirn.info

Im November und in der ersten Dezemberhälfte steht noch einmal das Schwerpunktthema **Künstliche Intelligenz** im Mittelpunkt, das in Kooperation mit der Gemeinnützigen Hertie-Stiftung erarbeitet wurde.

Das Schwerpunktthema **Struktur und Funktion neuronaler Netzwerke**, eine Themenpartnerschaft mit dem SFB 870, wurde um ein weiteres Videointerview ergänzt:

Struktur und Funktion: Neurone: Unterschiedliche Aufgaben brauchen unterschiedliche Zelltypen, die sich teilweise biophysikalisch sehr unterscheiden. Prof. Benedikt Grothe gibt eine Einführung, Prof. Alexander Borst zeigt am Sehsystem der Fliege eine zusätzliche Spezialisierung. Und dann sind da noch die Oligodendrozyten …

In dem Format **Frage an das Gehirn** beantworten Experten regelmäßig Fragen unserer Leser. Zuletzt ging es um die folgenden Fragen:

Wie funktioniert eine Vollnarkose? – Welche Wirkmechanismen lassen uns bei einer Vollnarkose die OP verschlafen?

Sind Gliazellen die eigentlichen Chefs im Gehirn? – Gliazellen hier, Gliazellen da … man könnte fast meinen, sie wären wichtiger als die Nervenzellen selbst. Wer hat denn nun das Sagen im Gehirn?

Reagiert der Körper auf's Wetter? – Woher kommt es, dass ich so wetterfühlig bin?

Gibt es neue Erkenntnisse zur Therapie bei Glioblastom? – Laut einem Ihrer Beiträge ist die Prognose bei Glioblastomen schlecht. Hat sich da in der Zwischenzeit etwas getan?

In der Rubrik **Neues aus der Wissenschaft** macht dasGehirn.info im November 2021 auf die folgenden Pressemeldungen aus den Instituten aufmerksam:

Insulin im Gehirn beeinflusst Dopamin-Spiegel | Deutsches Zentrum für Diabetesforschung (03.11.2021)

Besser sehen lernen | Ernst Strüngmann Institute (ESI) for Neuroscience in Cooperation with Max Planck Society (04.11.2021)

Marshmallow-Test bei Papageien | Max-Planck-Institut für Ornithologie (05.11.2021)

Damit das Warten nicht so schwerfällt | Ruhr-Universität Bochum (17.11.2021)

Die Angst im Gleichgewicht | Max-Planck-Institut für Neurobiologie (18.11.2021)

Spielend fürs Leben lernen | Max-Planck-Institut für evolutionäre Anthropologie (24.11.2021)

Wie Matrix-Recycling das Gehirn flexibel hält | Universitätsmedizin Göttingen (10.12.2021)

Möchten Sie eine Pressemeldung an dasGehirn.info weitergeben oder Ihr Institut vorstellen, wenden Sie sich bitte an Arvid Leyh (a.leyh@dasgehirn.info).

Neueintritte

Folgende Kolleginnen und Kollegen dürfen wir als Mitglieder der Neurowissenschaftlichen Gesellschaft begrüßen:

Janick Bartels (Oldenburg)
Marcos Caetano (Köln)
Umberto Calleri (Düsseldorf)
Felix Fiederling, Dr. (New York, USA)
Moritz Gerster (Leipzig)
Fernando Gonzalez Uarquin, Dr. (Mainz)
Johanna Hallenberger (Düsseldorf)
Sven Hendrix, Prof. Dr. (Hamburg)
Wenhui Huang, Dr. (Homburg)
Laura Jiménez Barrón (München)
Sabine Liebscher, Dr. Dr. (Martinsried)
Amanda Lima (Curitiba, Brasilien)
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Miriam Schillner (Mainz)
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Anna Josefine Torner (Hildesheim)
Linda Weiss, Dr. (Bochum)
Dieter Willbold, Prof. Dr. (Jülich)
Emile Wogram, Dr. (Cambridge, USA)
Alfred Yamoah (Aachen)

Der Mitgliedsstand zum 10. Dezember 2021 beträgt 2.059 Mitglieder.

Ausblick

Jonas Tesarz
Pain, the Brain and Sars-CoV2: Evidence for pain-specific alterations in brain-related structure-function-properties

Amit Agarwal & Manuela Simonetti
Glia adrenergic receptor signalling in neuropathic pain

Hans Georg Schaible
The role of neuroimmune interactions in musculoskeletal pain

Rohine Kuner & Herta Flor
Brain-based interventions for chronic pain

Angelika Lampert
Genetics meets Function in sodium channel-related pain disorders

NEUROWISSENSCHAFTLICHE GESELLSCHAFT
GERMAN NEUROSCIENCE SOCIETY

Neurowissenschaftliche Gesellschaft e.V. (NWG)

- Beitrittserklärung -

Hiermit erkläre ich meinen Beitritt zur Neurowissenschaftlichen Gesellschaft e.V. (NWG).

Eintrag in das Mitgliederverzeichnis:

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Ich unterstütze den Antrag auf Beitritt zur NWG e.V.

Datum/Unterschrift des Mitglieds Datum/Unterschrift des Mitglieds

Bitte senden Sie Ihren Antrag an die Geschäftsstelle der NWG:

Stefanie Korthals
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Ich optiere für folgende 2 Sektionen:

- ☐ Computational Neuroscience
- ☐ Entwicklungsneurobiologie/Neurogenetik
- ☐ junge NWG (jNWG)
- ☐ Klinische Neurowissenschaften
- ☐ Kognitive Neurowissenschaften
- ☐ Molekulare Neurobiologie
- ☐ Neuropharmakologie und -toxikologie
- ☐ Systemneurobiologie
- ☐ Verhaltensneurowissenschaften
- ☐ Zelluläre Neurobiologie

Ich bin Student ☐ ja ☐ nein
Ich bin ☐ weiblich ☐ männlich ☐ divers
Geburtsjahr _____

☐ **Ich erkläre mich einverstanden**, dass meine Daten zum Zwecke wissenschaftlicher Informationsvermittlung (z.B. **FENS-Mitgliedschaft**) weitergegeben werden.
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- ☐ 80,– €/Jahr Postdocs (PhD, Dr., etc.)
- ☐ 40,– €/Jahr Studenten, Doktoranden, Mitglieder in Elternzeit oder im Ruhestand, Arbeitslose

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