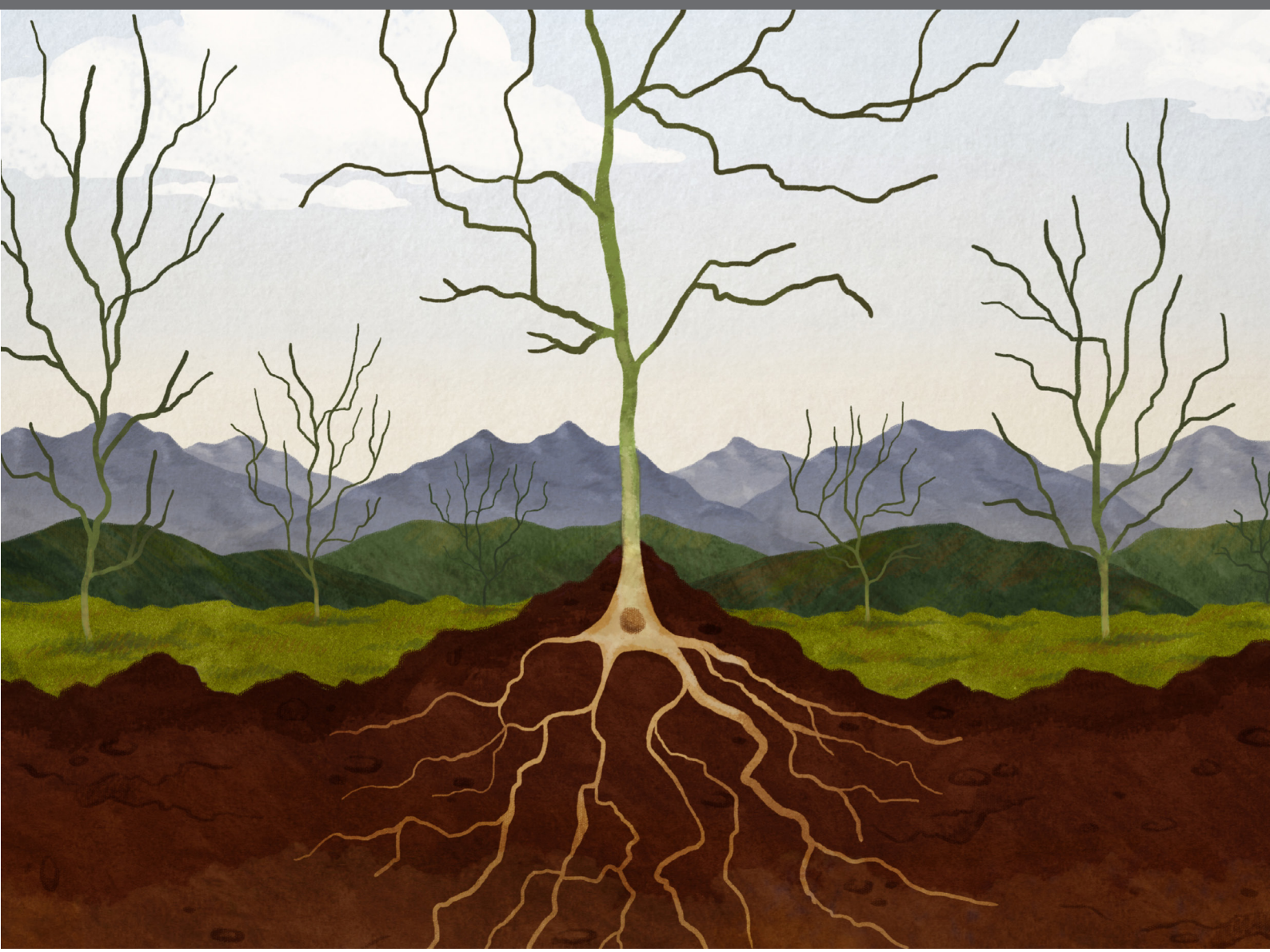
FROM ECOLOGY TO BRAIN DEVELOPMENT: BRIDGING SEPARATE EVOLUTIONARY PARADIGMS

EDITED BY: Francisco Aboitiz, Miguel L. Concha, Christian González-Billault and Jorge Mpodozis

PUBLISHED IN: Frontiers in Neuroscience



frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88945-557-7
DOI 10.3389/978-2-88945-557-7

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

FROM ECOLOGY TO BRAIN DEVELOPMENT: BRIDGING SEPARATE EVOLUTIONARY PARADIGMS

Topic Editors:
Francisco Aboitiz, Pontificia Universidad Católica de Chile, Chile
Miguel L. Concha, Universidad de Chile, Chile; Biomedical Neuroscience Institute, Chile; Geroscience Center for Brain Health and Metabolism (GERO), Chile
Christian González-Billault, Universidad de Chile, Chile; Geroscience Center for Brain Health and Metabolism (GERO), Chile; The Buck Institute for Research on Aging, United States
Jorge Mpodozis, Universidad de Chile, Chile

The illustration is an artistic drawing that depicts a pyramidal neuron planted on the earth as if it was a tree, with its apical dendrites representing the stem and the cell body and basilar dendrites making up the roots. Implicit in the drawing is our attempt to bridge the nervous system with its surrounding environment, as is stated in the eBook's title. Drawing was made by artist Isabel Guerrero, who owns the copyright.

The nervous system is the product of biological evolution and is shaped by the interplay between extrinsic factors determining the ecology of animals, and by intrinsic processes that dictate the developmental rules that give rise to adult functional structures. This special topic is oriented to develop an integrative view from behavior and ecology to neurodevelopmental processes. We address questions such as how do sensory systems evolve according to ecological conditions? How do neural networks organize to generate adaptive behavior? How does cognition

and brain connectivity evolve? What are the developmental mechanisms that give rise to functional adaptation? Accordingly, the book is divided in three sections, (i) Evolution of sensorimotor systems; (ii) Cognitive computations and neural circuits, and (iii) Development and brain evolution. We hope that this initiative will support an interdisciplinary program that addresses the nervous system as a unified organ, subject to both functional and developmental constraints, where the final outcome results of a compromise between different parameters rather than being the result of several single variables acting independently of each other.

Citation: Aboitiz, F., Concha, M. L., González-Billault, C., Mpodozis, J., eds (2018). From Ecology to Brain Development: Bridging Separate Evolutionary Paradigms. Lausanne: Frontiers Media. doi: 10.3389/978-2-88945-557-7

Table of Contents

frontiers in Neuroscience

EDITORIAL
published: 29 June 2018
doi: 10.3389/fnins.2018.00447

Editorial: From Ecology to Brain Development: Bridging Separate Evolutionary Paradigms

Francisco Aboitiz[1]*, *Miguel L. Concha*[2,3,4], *Christian González-Billault*[4,5,6] and *Jorge Mpodozis*[7]

[1] Centro Interdisciplinario de Neurociencias, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile, [2] Faculty of Medicine, Institute of Biomedical Sciences, Universidad de Chile, Santiago, Chile, [3] Biomedical Neuroscience Institute, Santiago, Chile, [4] Geroscience Center for Brain Health and Metabolism, Santiago, Chile, [5] Laboratory of Cell and Neuronal Dynamics, Department of Biology, Faculty of Sciences, Universidad de Chile, Santiago, Chile, [6] The Buck Institute for Research on Aging, Novato, CA, United States, [7] Laboratorio de Neurobiología y Biología del Conocer, Departamento de Biología, Facultad de Ciencias, Universidad de Chile, Santiago, Chile

Keywords: critical periods, computational neuroscience, visual perception, microcircuits, homology, birds, cerebral cortex, olfaction

Editorial on the Research Topic

From Ecology to Brain Development: Bridging Separate Evolutionary Paradigms

OPEN ACCESS

Edited by:
Paul J. Watson,
University of New Mexico,
United States

Reviewed by:
Chiaki Ohtaka-Maruyama,
Tokyo Metropolitan Institute of Medical Science, Japan

***Correspondence:**
Francisco Aboitiz
faboitiz@puc.cl

Specialty section:
This article was submitted to Social and Evolutionary Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *04 May 2018*
Accepted: *12 June 2018*
Published: *29 June 2018*

Citation:
Aboitiz F, Concha ML, González-Billault C and Mpodozis J (2018) Editorial: From Ecology to Brain Development: Bridging Separate Evolutionary Paradigms. Front. Neurosci. 12:447. doi: 10.3389/fnins.2018.00447

This special topic proposes an integrative view of brain evolution involving ecology, behavior, cognition and neurodevelopmental processes. We address three main questions, (i) the role of sensorimotor systems in brain evolution, (ii) the evolution of computational capacities and neural circuits, and (iii) the role of development in shaping brain evolution.

EVOLUTION OF SENSORIMOTOR SYSTEMS

The organism interacts with the environment through a sensory-motor interface, which is critical for driving evolutionary change. Pallas discusses the relation between embryonic processes that build up sensory processing structures in mammals, and the selection of specific developmental pathways yielding adaptive neuronal networks. Pallas focuses on critical periods of sensory development, where more rigid phenotypes may be selected in predictable environments while developmental flexibility is favored in conditions of unpredictability. Wylie et al. address the evolution of the visual system in birds in the context of sensory adaptations of different species. For example, components of the accessory optic system involved in the analysis of optic flow are particularly developed in hummingbirds, while the Wulst, a brain component supporting binocular vision, is enlarged in frontal looking species like owls. Aboitiz and Montiel focus on the role of olfaction in the origin of the mammalian neocortex. The latter is proposed to develop as an interface between olfactory and hippocampal networks involved in navigation, recruiting additional sensory inputs into this orientation network. Aboitiz then discusses the evolutionary origin of the human speech networks, from the peripheral control of the vocal system to the central networks controlling auditory-vocal coordination. A key innovation in human evolution is the development of an auditoy-vocal cortical network that increases vocal working memory and vocal learning capacity. Ending this section, Ravignani reviews the topic of behavioral antisynchrony in interindividual coordination, as seen in two disparate species: fiddler crabs and human infants. Ravignani proposes a broad framework to interpret these behaviors, relying on the evolution of perceptual biases driving animals toward rhythmic coordination.

COGNITIVE COMPUTATIONS AND NEURAL CIRCUITS

A second level is the generation of internal processing devices that modulate the relation between perception and behavior. King discusses the ecological underpinnings of cognitive computation, warning that computational analogies of the human mind are rooted in the early conceptual work of George Boole, long before the technological digital revolution came to be. In a different approach, Bosman and Aboitiz take issue with the extended conservation of brain microcircuits, from crayfish to mammals. Canonical microcircuits can be described in several taxa and neural systems, consisting of input-receiving neurons, output neurons and excitatory and inhibitory interneurons that regulate the balance between excitation and inhibition in larger neural networks. Finally, Faunes et al. discuss homology of brain components across species, arguing that hodology (neural connectivity) is the most relevant criterion to establish homologies, as opposed to genetic criteria. As a critical example, they propose homology between a globular brain structure termed dorsal ventricular ridge (DVR) in reptiles/birds, and parts of the six-layered mammalian neocortex, on the basis that similar sensory projections ascending from brainstem nuclei synapse in both structures.

DEVELOPMENT AND BRAIN EVOLUTION

Evolution is a sequence of ontogenies rather than of adult states, and change must take place through developmental transformations. In contrast to the hodological perspective mentioned above, some studies propose non-homology between the neocortex and the DVR, as they derive from different embryonic components, the dorsal and the ventral pallium respectively. Instead of focusing on embryonic compartments, Montiel and Aboitiz look for underlying developmental mechanisms that modulate brain patterning in reptiles/birds and mammals, proposing differential regulation of specific morphogenetic signals in these two groups. The laminar mammalian neocortex would have developed from upregulation of morphogens originating in the dorsal hemisphere, while in reptiles/birds these factors remained downregulated yielding a globular DVR. Other patterning signals like the gene Pax6 are modulated in both groups. Luzzati also touches on the problem of the origin of the mammalian neocortex, evidencing a similarity between cellular phenotypes in superficial neocortical layers with those found in reptilian brains. Luzzati argues for a superposition between the dorsal cortex and the olfactory cortex in the evolutionary emergence of the neocortex. In the last article in this section, Salas et al.discuss ontogenetic brain scaling in lampreys, one of the two living jawless vertebrates. Salas and collaborators assess brain and body growth in the lamprey's ontogeny, in order to test the hypothesis that the developmental transitions in behavior are related to distinct events in the development of specific brain components. Particularly, brain size increases markedly in the metamorphosis, as opposed to body size that remains unchanged in this process.

Our aim in this Topic has been to show research that bridges two approaches that have been difficult to reconcile, one that focuses on the evolution of behavior and brain function, and the other that is concerned with the developmental mechanisms involved in the production of new phenotypes. The presumed homology between the mammalian neocortex and the reptilian/avian DVR is an eloquent example of this, being perhaps the most controversial problem of modern comparative neuroanatomy. In one perspective, (i) there was transformation of an ancestral DVR-like structure into a cortical, layered morphology during mammalian evolution, concomitant with (ii) a topographic reorganization of the embryonic brain to place the DVR adjacent to the dorsal pallium (Faunes et al.). In the other perspective, (i) the neocortex and the DVR are not comparable because they belong to different embryonic components, and (ii) mesencephalic sensory axons were redirected in mammals from a ventral position into the dorsal pallium where the neocortex develops. While Montiel and Aboitiz favor the second proposal, both scenarios may be compatible with an increase in dorsalization signals that impose a laminar organization to the mammalian neocortex.

We hope that this initiative will contribute to view the nervous system as a unified system, subject to both functional and developmental constraints, where evolution results from the interplay of these different factors.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

REVIEW
published: 28 June 2017
doi: 10.3389/fnins.2017.00344

The Impact of Ecological Niche on Adaptive Flexibility of Sensory Circuitry

Sarah L. Pallas *

Neuroscience Institute, Georgia State University, Atlanta, GA, United States

Evolution and development are interdependent, particularly with regard to the construction of the nervous system and its position as the machine that produces behavior. On the one hand, the processes directing development and plasticity of the brain provide avenues through which natural selection can sculpt neural cell fate and connectivity, and on the other hand, they are themselves subject to selection pressure. For example, mutations that produce heritable perturbations in neuronal birth and death rates, transcription factor expression, or availability of axon guidance factors within sensory pathways can markedly affect the development of form and thus the function of stimulus decoding circuitry. This evolvability of flexible circuits makes them more adaptable to environmental variation. Although there is general agreement on this point, whether the sensitivity of circuits to environmental influence and the mechanisms underlying development and plasticity of sensory pathways are similar across species from different ecological niches has received almost no attention. Neural circuits are generally more sensitive to environmental influences during an early critical period, but not all niches afford the same access to stimuli in early life. Furthermore, depending on predictability of the habitat and ecological niche, sensory coding circuits might be more susceptible to sensory experience in some species than in others. Despite decades of work on understanding the mechanisms underlying critical period plasticity, the importance of ecological niche in visual pathway development has received little attention. Here, I will explore the relationship between critical period plasticity and ecological niche in mammalian sensory pathways.

Keywords: sensory deprivation, cross-modal plasticity, topographic maps, synaptic plasticity, inhibitory plasticity

OPEN ACCESS

Edited by:
Jorge Mpodozis, Universidad de Chile, Chile

Reviewed by:
Alfredo Kirkwood, Johns Hopkins University, United States
Hey-Kyoung Lee, Johns Hopkins University, United States

***Correspondence:**
Sarah L. Pallas
spallas@gsu.edu

Specialty section:
This article was submitted to Evolutionary Psychology and Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *16 January 2017*
Accepted: *01 June 2017*
Published: *28 June 2017*

Citation:
Pallas SL (2017) The Impact of Ecological Niche on Adaptive Flexibility of Sensory Circuitry. Front. Neurosci. 11:344. doi: 10.3389/fnins.2017.00344

"... evolution is the control of development by ecology." -*Leigh van Valen*

DEVELOPMENT BOTH FACILITATES AND CONSTRAINS ADAPTATION

Early events in nervous system development are very similar across species because they provide a basic framework upon which more species-specific events are built at later time points. Mutations that affect early events are likely to be deleterious or even lethal, and thus they place severe constraints on potentially adaptive variation. If they are not deleterious, early changes could produce profound alterations in structure and function, affecting any circuitry that is dependent on that early framework. Mutations that occur later in nervous system development would have less of

an effect, but because of the interconnected nature of neurons, even small changes in one member of a network will affect all members of the network. This is a potentially dangerous situation, and thus evolution has come up with work-arounds that can preserve neural network function despite the unavoidable missteps that can occur in brain building. Many of those work-arounds involve built-in flexibility that allows networks to adapt to variation within a lifetime as well as across evolutionary time, thus facilitating adaptation.

TARGET SPECIFICITY

One of the most critical steps in building neural circuits is for axons to locate and make synapses within the proper target. At one extreme, each axon could have its target choices pre-specified. This was the premise behind Sperry's chemoaffinity hypothesis. When he cut the optic nerve and rotated the eye of a frog, the axons within the optic nerve regenerated and made synapses with their original target sites in the optic tectum, leading to frogs that made 180° errors in locating visual stimuli. These results suggested to Sperry that there is a chemical address system in which axons and targets have matching labels that they use to find each other in a proverbial haystack.

Sperry's findings suggested that evolution had provided a strict one to one wiring diagram for the brain. What Sperry didn't realize is that frogs can eventually make corrections in their retinotectal wiring, correcting their visual localization ability. Similarly, Xenopus tadpoles, which have binocular vision as a result of the intrahemispheric connections of the nucleus isthmi, can realign those connections after eye rotation (Udin and Keating, 1981; Udin, 2012, for review). In an extreme example, a third eye primordium transplanted onto a tadpole's head can successfully compete with the existing eyes for target space in the optic tectum. The extra eye drives the formation of eye-specific termination regions that resemble the ocular dominance stripes seen normally in binocular visual cortex of carnivores and primates (LeVay et al., 1978, 1980; Law and Constantine-Paton, 1981). In contrast to Sperry's more rigid chemoaffinity hypothesis, these findings illustrate the power of visual experience to guide not only normal connectivity patterns between eye and brain, but to compensate for unique circumstances in a way that optimizes function.

When initially considered the corrections to retinotectal maps in frogs seem quite remarkable. However, the wiring of input and target neurons is normally shaped by experience to some extent. The "fire together, wire together" and "use it or lose it" principles of Hebbian learning (Hebb, 1949) can account for experience-dependent changes in the strength and maintenance of synaptic connections. NMDA receptors allow activity levels to be translated into synaptic strength (Constantine-Paton and Cline, 1998). Even before eye opening, spontaneous activity that resembles visually driven activity occurs at several points within the visual pathway (Meister et al., 1991; Weliky and Katz, 1999; Chiu and Weliky, 2001) and can guide normal circuit wiring to a considerable extent. This is important when considering that the point at which birth and eye opening occur with respect to gestation varies across species. Thus, in more altricial, nocturnal, and fossorial species, spontaneous activity may be a more important factor than in precocial, diurnal, cursorial species in shaping connectivity relative to vision.

CROSS-MODAL PLASTICITY

Another illustration of the extent to which axons can be flexible in their target choice comes from studies of cross-modal plasticity in sensory cortex. Cerebral cortex develops in a stepwise fashion (**Figure 1**), beginning from an undifferentiated, laminated sheet with common features throughout. Regional information is established under the control of various transcription factors and morphogens, some of which are arranged in opposing gradients (Puelles and Rubenstein, 2003; Ypsilanti and Rubenstein, 2016). How precise boundaries form between adjacent cortical areas is not well-understood. The formation of area-specific modules, such as cytochrome oxidase blobs and ocular dominance

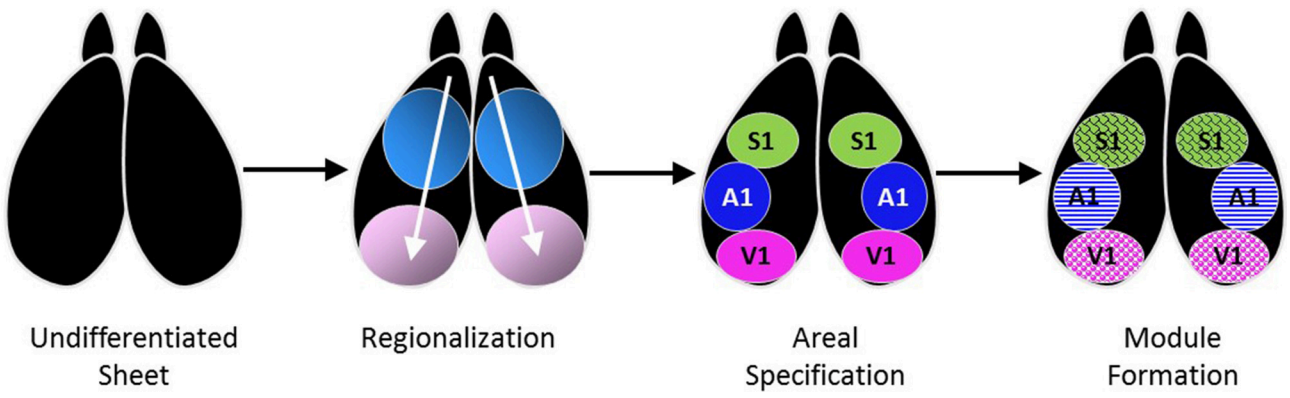


FIGURE 1 | Specification of primary sensory areas in cerebral cortex occurs gradually, starting with establishment of positional identity and polarity gradients that lead to regionalization, followed by formation of strict boundaries between cortical areas and the thalamocortical projections that bring in sensory information. Within each area, modules for special processing are distributed in a pattern that is characteristic for each area (Modified from Pallas et al., 2006, used with permission).

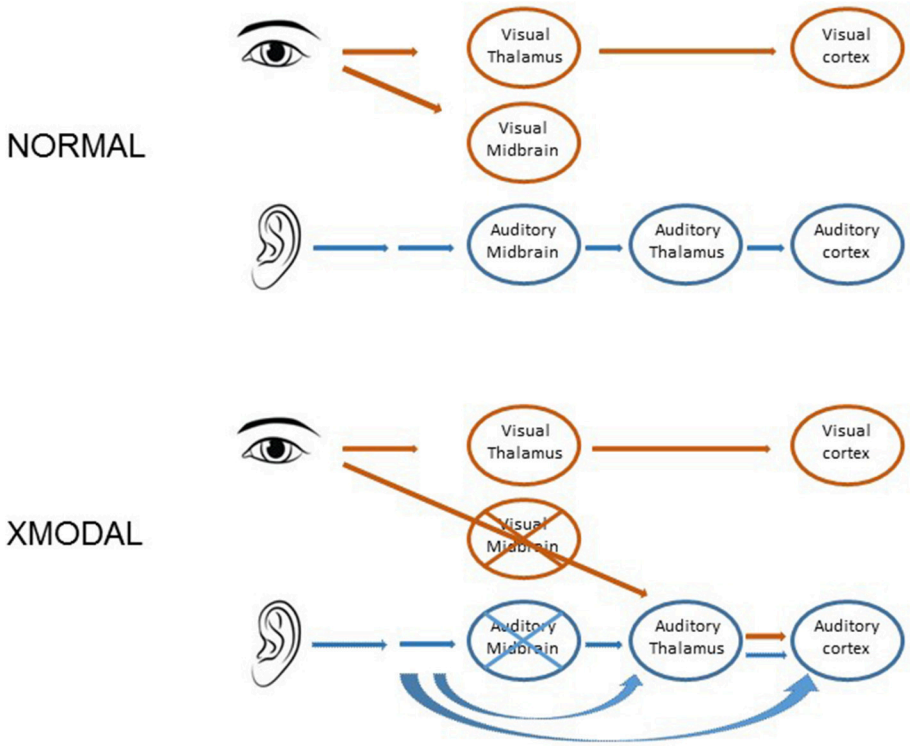


FIGURE 2 | Cartoon depicting the normal projections in the auditory and visual pathways **(top)** and the surgical procedure that leads to cross-modal plasticity in ferrets **(bottom)**. As a result of the procedure, the retina invades the auditory thalamus, which in turn conveys visual activity to the auditory cortex.

columns in primary visual cortex (V1) (LeVay et al., 1978; Trusk et al., 1989), binaural bands in primary auditory cortex (A1) (Middlebrooks et al., 1980), and whisker barrels in primary somatosensory cortex (S1) (Woolsey and Van der Loos, 1970), occurs under the partial direction of neural activity. Studies of cross-modal plasticity investigate the extent to which these area-specific features are flexible.

In hamsters, mice, and ferrets, neonatal damage to the sensory midbrain, which reduces retinal target space and deafferents some sensory thalamic regions, can induce retinal axons to invade non-visual targets, including the auditory thalamus and the somatosensory thalamus (Schneider, 1973; Frost, 1982; Sur et al., 1988; Ellsworth et al., 2005). In ferrets, midbrain damage results in a partial takeover of auditory thalamus and auditory cortex by visually driven activity (**Figure 2**). The circuitry within auditory cortex is altered in response, such that auditory cortical responses to light stimuli resemble those in visual cortex, including the presence of a two-dimensional map of visual space (Sur et al., 1988; Roe et al., 1990, 1992; Pallas and Mao, 2012, for review). Callosal and local connectivity patterns were altered and reorganized in a way that suggested a splitting of the auditory cortical area into segregated auditory and visual subareas (Gao and Pallas, 1999; Pallas et al., 1999). To the contrary, we discovered that although auditory responses remain, tuning to sound frequency is broader, the tonotopic map is virtually absent (**Figure 3**), and sound-responsive neurons have

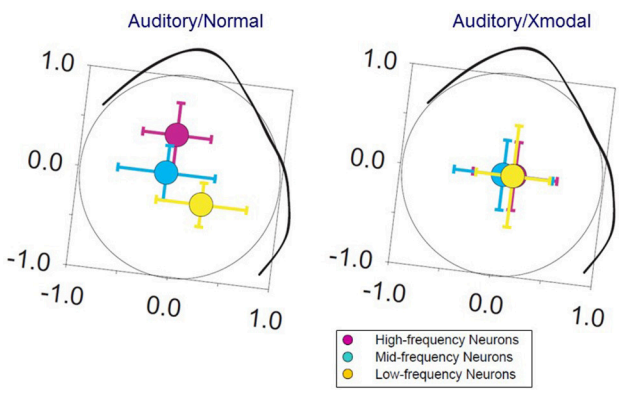


FIGURE 3 | Tonotopic maps in normal ferrets are oriented such that high frequencies are represented medially and low frequencies laterally **(left)**. In auditory cortex of ferrets in which retinal axons have invaded auditory thalamus, visually-responsive, sound-responsive, and bisensory neurons are intermixed **(right)**. The tonotopic map in these ferrets is absent, with no significant difference in the spatial center of distribution (colored circles) of high, medium, or low-frequency tuned neurons (error bars indicate ± standard error. Modified from Mao and Pallas, 2012, used with permission).

higher thresholds in cross-modal auditory cortex, perhaps due to changes in organization of inhibitory interneurons (Mao et al., 2011b; Mao and Pallas, 2012, 2013). In addition, multisensory

neurons that respond to either sound or light stimulation are created at the expense of sound-only neurons. The number of visual-only neurons increases with the extent of the early damage. These results show that, although the cerebral cortex is quite flexible in its ability to accommodate various types of inputs, there is a limit to the ability to do two things at once, at least in primary auditory cortex. The difficulty may be one of topography. In multisensory cortical regions that do successfully represent two modalities, they share a common topographic basis—such as location of an auditory or visual stimulus in space (Wallace et al., 1992, 2006). In primary auditory cortex, there is no map of stimulus location; rather it contains a map of sound frequency. The two dimensional map of visual space created in cross-modal primary auditory cortex (Roe et al., 1990) may interfere with the one-dimensional map of frequency, and thus with a major organizing principle of A1, leading to the degradation of tuning that we observed.

Cross-modal plasticity may seem an extreme response to loss of input or target space only obtained through special experimental circumstances. This is far from being true; cross-modal plasticity in the form of sensory substitution occurs both evolutionarily and clinically. Animals with evolutionarily reduced visual input, such as blind cave fish (Hinaux et al., 2016) or blind mole rats (Heil et al., 1991; Bronchti et al., 2002) exhibit a takeover of the underutilized visual regions by other senses. On a developmental time scale, in deaf or blind animals including humans, the intact sense takes over territory that would normally belong to the deprived or damaged sense. This produces what can seem like supernatural ability in the intact sense (Rauschecker et al., 1992; Rauschecker and Korte, 1993; Bavelier and Neville, 2002; Lomber et al., 2010; Butler et al., 2017; Glick and Sharma, 2017; Kral et al., 2017; Schormans et al., 2017). The ability of sensory cortex to reconfigure its organization and connectivity according to unforeseen circumstances would predispose it to adapt to evolutionary change (Pallas, 2007; Kral and Pallas, 2011; Pallas and Mao, 2012, for review).

POPULATION MATCHING AND CELL DEATH

Another way in which developmental mechanisms can predispose circuits to accommodate new afferents, allow innervation of new target space, and compensate for changes in either population is through flexible population matching mechanisms. Many more neurons are generated in early development than survive until adulthood, and survival of afferents can be affected by availability of target space (Hamburger and Levi-Montalcini, 1949; Hollyday and Hamburger, 1976). The reverse is also true; target neurons are dependent upon innervation for survival (Pallas et al., 1988; Buss et al., 2006). Furthermore, the interconnectedness of brain pathways means that a change in number of neurons in one region will affect all members of the pathway like a stack of dominoes. The evolutionary benefit is that a mutation that increases or decreases the number of neurons at one locus of a pathway will be accommodated through changes in neuron survival or alterations in branching at every level of the pathway.

The more connectivity options that a neuron has, the less it will be affected by a decrease in target size (Finlay and Pallas, 1989, for review). For example, retinal axons have many potential targets, and if one is lost, the axons will increase their projections to alternate targets, even to other modalities (**Figure 2**). On the other hand, some brain regions receive input from or send inputs to only a single other region. One example is the lateral geniculate nucleus (LGN), which requires primary visual cortex (V1) in order to survive. Ablation of V1 leads to massive cell death in LGN (Raabe et al., 1986; Woo et al., 1992), but ablation of large portions of thalamus has little impact on cerebral cortex (Miller et al., 1991) due to the many alternate synaptic partners for cortical neurons. From an evolutionary perspective, singly targeted afferent populations seem risky. One might speculate that the cost is lower than the benefit of having a dedicated communication channel between sensory thalamus and primary sensory cortices.

POPULATION MATCHING IN TOPOGRAPHIC MAPS

Whether a decrease in target size affects function has been addressed in studies of topographic map compression. In adult frogs and fish, ablation of the caudal half of the optic tectum results in a compression of the regenerating retinal axons onto the remaining half (Udin, 1977; Schmidt, 1983). Although, the optic nerve in adult mammals does not regenerate without heroic efforts (Bei et al., 2016; Lim et al., 2016), it can regenerate in neonatal hamsters (Finlay et al., 1979) and mice (Pallas, in preparation). Map compression in neonatal hamsters occurs without substantial increases in retinal cell death (Wikler et al., 1986), such that a 50% lesion of the superior colliculus (SC) leads to a doubling of the input/target ratio. Remarkably, this occurs without a concomitant increase in SC neuron receptive field size (Pallas and Finlay, 1989). The preservation of receptive field size is achieved by a reduction in retinal axon arbor complexity and by a selective redirection of some retinal axons to alternate target regions (Pallas and Finlay, 1991; Xiong et al., 1994). This result implies that the SC neurons have a way to recognize how much visual space is represented by the retinal ganglion cells competing for target space. Thus, despite having twice as many retinal afferents available to them, SC neurons select only those that represent the same amount of visual space as in normal, non-compressed maps. We tested the hypothesis that, although the compression itself is activity-independent, NMDA receptors on the SC neurons could provide a filter for the degree of receptive field overlap of the competing retinal inputs. Chronic blockade of NMDA receptors in SC during post-natal development prevented the normal refinement of receptive fields, as seen in other species (Debski et al., 1990; Schmidt et al., 2000). It also blocked the compensation process for map compression, leading to receptive fields within the compressed maps that were even larger than in normal juveniles (Huang and Pallas, 2001), supporting the hypothesis.

The changes in axon arbor complexity might be expected to degrade stimulus tuning. As in the "bug detector" neurons in frog optic tectum (Lettvin et al., 1959), neurons in superficial SC of rodents are tuned to stimulus size and velocity, preferring small, slowly moving objects (Razak and Pallas, 2005, 2006). In animals that have undergone map compression, stimulus size tuning, and stimulus velocity tuning of the population of SC neurons are normal (Pallas and Finlay, 1989). NMDA receptor blockade had no effect on size or velocity tuning (Huang and Pallas, 2001; Razak et al., 2003). Instead, an increase in the strength and spatial extent of lateral inhibition in compressed maps apparently compensates for the excess retinal inputs in a way that preserves stimulus tuning properties (Razak and Pallas, 2007; Razak et al., 2010). That receptive field properties remain stable even for massive changes in afferent/target ratios makes a powerful argument that developmental mechanisms can predispose the brain to accommodate evolutionary changes in neuron population numbers.

Given that gradients of the repulsive guidance factors ephrin-A2 and -A5 in the SC and their EphA receptors in the retina are responsible for setting up the topographic map in normal SC (Feldheim et al., 2000, 2004; Cang et al., 2005), we reasoned that they might also be responsible for map compression. Our correlative gene expression study supported this hypothesis; SC size after neonatal lesion correlates not only with the steepness of the retino-SC map, but also with the steepness of the ephrin-A2 and eprhin-A5 gradients (Tadesse et al., 2013). Preliminary data with ephrinA knockout mice (kindly donated by David Feldheim and Renping Zhou) are consistent with the hypothesis that ephrinAs are necessary for the retino-SC maps to compress (Mao et al., 2011a, and in preparation; **Figure 4**). Whether the early damage to SC that triggers the map compression is first triggering the redistribution of ephrin-As or vice versa is unknown, and is currently under study. At any rate, regulation of guidance cue distribution by the size of the brain region would be another developmental process that could accommodate evolutionary change in an adaptive way.

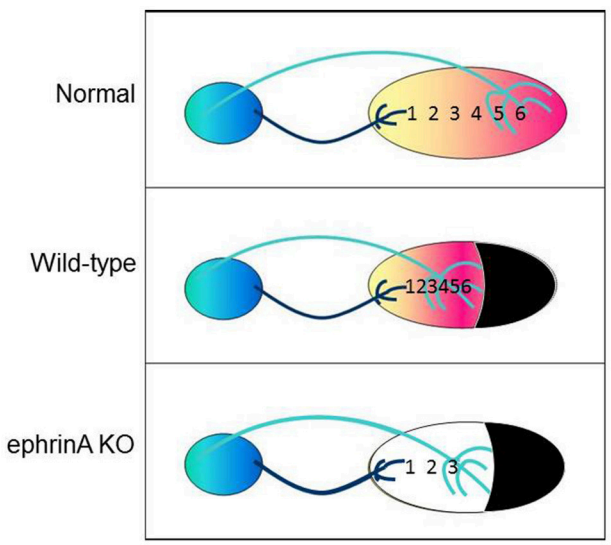


FIGURE 4 | Cartoon illustrating the mapping of nasal to temporal visual field locations 1–6 onto the anterior to posterior axis of SC in normal animals **(top)**, in animals with compression of the entire visual field onto the smaller SC after neonatal ablation of caudal SC **(middle)**, and in ephrin knockout animals that failed to compress their retino-SC projections **(bottom)**.

RECEPTIVE FIELDS ARE THE CURRENCY THAT SENSORY NEURONS USE TO REPRESENT THE STIMULUS SPACE

The "classical" receptive field (RF) derives from the spatiotemporal sum of visually responsive excitatory and inhibitory inputs (Allman et al., 1985). RF size is an important contributor to visual acuity; neurons with large RFs are better at motion decoding and worse at decoding spatial fine structure than neurons with small RFs (Livingstone and Hubel, 1988; Blakemore, 1990; Levitt et al., 2001). RFs are large at birth, and undergo a postnatal refinement process to reach adult size. It has been assumed, based largely on studies of ocular dominance (OD) in primary visual cortex (V1) of cats and monkeys (Hensch et al., 1998; Espinosa and Stryker, 2012), that visual pathway development requires early visual experience during a critical period for maturation but not for maintenance of refined circuitry. Evidence from experiments in both SC (Carrasco et al., 2011; Balmer and Pallas, 2015b) and V1 (e.g., Huang et al., 1999; Fagiolini and Hensch, 2000; van Versendaal et al., 2012) suggests a signaling pathway that involves TrkB receptors. Visual experience activates NMDA receptors, which allow calcium entry into the neuron and activation of CaMKII. This signaling pathway promotes BDNF transcription, leading to TrkB-mediated alterations in GABAergic inhibition (Hong et al., 2008; Lin et al., 2008; Bloodgood et al., 2013; Park and Poo, 2013; Spiegel et al., 2014). This in turn promotes increased inhibition from fast-spiking, GABAergic "basket" type neurons. Mature basket cells and their proteoglycan-rich perineuronal nets (PNNs) enwrap the somata of glutamatergic pyramidal neurons, resulting in reduced plasticity and thus closure of the critical period for ocular dominance plasticity (Bavelier et al., 2010; Beurdeley et al., 2012). Most mammals do not have ocular dominance columns, however, and neither pyramidal nor basket neurons are found outside of the telencephalon (Jones and Hendry, 1984; Peters and Jones, 1984), suggesting that the proposed mechanism may not be generalizable across different brain regions, species, or types of plasticity. An alternative mechanism places maturation of PSD-95-dependent, "silent" synapse maturation as the necessary and sufficient step in critical period plasticity (Huang et al., 2015). PSD-95 anchors glutamate receptors at the postsynaptic density, promoting stability of excitatory glutamatergic synapses in neocortex and hippocampus (Liao et al., 2001; Lüscher and Malenka, 2012).

USE-DEPENDENT PLASTICITY

Excitatory and inhibitory synaptic connections can be made stronger with use and weaker with disuse (Hebb, 1949; Stent,

1973; Quinlan et al., 1999; Philpot et al., 2001; Castillo et al., 2011; Sanes and Kotak, 2011; Trachtenberg, 2015). The threshold for induction of plasticity increases with age (Kirkwood et al., 1995). As a result, use-dependent excitatory and inhibitory plasticity provides flexibility early in life, and stability later. Sensory experience has a powerful influence on the development and plasticity of neural circuits (Munz et al., 2014). Shaping connectivity under the direction of sensory inputs ensures that circuits are tuned to the environment on both developmental and evolutionary time scales. Thus, environmental changes can be incorporated in circuits in an ecologically adaptive way by existing developmental processes.

Not all activity generated in sensory pathways comes from the outside world. Neurons also fire spontaneous action potentials. Spontaneous activity can be highly organized, to the extent that it mimics sensory inputs. Before eye opening, waves of nicotinic acetylcholine-based and then glutamate-based spontaneous activity wash over the retina (Wong et al., 1993; Feller, 2002; Arroyo and Feller, 2016). Due to the retinotopic organization of the visual pathway, these waves will activate neighboring neurons that represent adjacent regions of the visual field. When the eyes open, spontaneous activity declines and is replaced by visually driven activity. Birth and eye opening are uncoupled (Clancy et al., 2001, 2007), however, and exposure to visual experience varies with niche, so some species may rely on visual drive for shaping their visual pathways more than other species.

Whether driven by light or by waves of spontaneous activity, coincident excitation of neighboring neurons that converge on a common target neuron increases the likelihood that the target neuron will fire an action potential. If there are NMDA receptors on the target neuron, there is also a greater likelihood that calcium entry will activate CaMKII and the signaling pathway that leads to insertion of AMPA receptors in the postsynaptic membrane, stabilizing the connections and increasing the synaptic strength (Cline and Constantine-Paton, 1989; Constantine-Paton and Cline, 1998). As a result, even without open eyes, the visual pathway is refined based on the neurons that exhibit the highest degree of cooperative activity (McLaughlin et al., 2003). The question then arises about the relative importance of spontaneous vs. sensory-driven activity in development of sensory pathways.

CRITICAL PERIODS

Critical periods allow developing visual circuits to be modified permanently by the environment while providing stable circuitry later in life. Although, spontaneous activity plays an important early role (Kirkby et al., 2013), the dominant view, based largely on studies of ocular dominance plasticity in carnivore and primate visual cortex, contends that visual experience within an early critical period is necessary for maturation and that beyond this period, plasticity is minimal (Espinosa and Stryker, 2012). Our results in hamster SC challenge this view derived from ocular dominance plasticity studies. We find that developmental refinement of visual receptive field (RF) size in both SC and V1 occurs *without visual experience* (**Figures 5A**$_{1,2}$,**5B**$_{12-14}$), but that continued dark rearing results in a loss of RF refinement in adulthood (>P60 days) (**Figures 5A**$_{3}$,**5B**$_{15}$; Carrasco et al., 2005; Balmer and Pallas, 2015a). A brief, late juvenile exposure to light stabilizes receptive field size permanently (**Figures 5A**$_{6-10}$, **5B**$_{16}$), but visual experience after postnatal day (P) 60 has no effect (**Figure 5A**$_{4,5,11}$; Carrasco and Pallas, 2006; Balmer and Pallas, 2015a). Interestingly, V1 requires a longer period of late juvenile light exposure to stabilize small RFs than SC (compare **Figure 5A**$_{10}$ and **Figure 5B**$_{16,17}$). These unexpected results refute the hypothesis that subcortical and cortical regions differ in their dependence on vision, and raise the interesting possibility that the current paradigm, derived from classic lab animal models, does not generalize across species, areas, and/or response properties. Other evidence supports this possibility. For example, adult visual cortex is more plastic in mice than cats (Sawtell et al., 2003; Espinosa and Stryker, 2012; Hübener and Bonhoeffer, 2014), and there are species differences in the susceptibility of orientation tuning to early experience. Inhibition is important in gating cortical plasticity in general (Artola and Singer, 1987). It has been proposed that activation of synaptic inhibition in the developing visual cortex is responsible for opening the critical period for ocular dominance plasticity (Hensch et al., 1998; Iwai et al., 2003). Closing it is thought to result from a maturation of

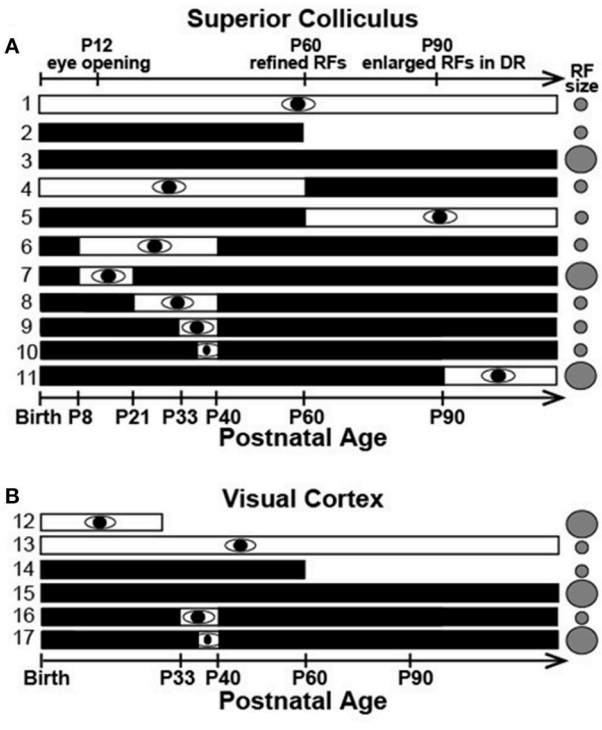


FIGURE 5 | Summary of previous data on timing of RF refinement and sensitivity to visual deprivation. Refinement occurs normally in the dark but late postnatal visual experience is required to maintain adult RFs in both **(A)** SC and **(B)** V1. White and black bars indicate timing of light and dark rearing, respectively. Gray circles indicate adult RF size (Modified from Balmer and Pallas, 2015a, used with permission).

GABAergic synapses (Huang et al., 1999; Jiang et al., 2005) that is driven by excitatory inputs (Kuhlman et al., 2013; Gu et al., 2016). Alternatively, there is some evidence for a more critical role of silent synapse maturation in critical period timing (Huang et al., 2015).

THE ROLE OF VISION IN BEHAVIOR DIFFERS AMONG SPECIES

The segregation of parallel visual pathways into dorsal "What" and ventral "Where" streams is conserved across primates, carnivores, and rodents (Waleszczyk et al., 2004; Van den Bergh et al., 2010; Wang et al., 2012), but there is tremendous variation across species in the role of vision in survival and behavior (Wilson and Reeder, 2005; Myers et al., 2014; Veilleux and Kirk, 2014). Optics, photoreceptor density, and receptive field size/overlap provide anatomical and physiological limits on acuity (Parker and Hawken, 1985; Troilo et al., 1996; Kaskan et al., 2005; Bleckert et al., 2014). Clearly, species that are more active at night will have limited access to visual information compared to diurnal species. Considerable evidence exists for a linkage between visual acuity and diel activity pattern, with diurnal species having larger eyes/retinae, higher numbers of photoreceptors, and higher visual acuity (Wikler and Rakic, 1996; Veilleux and Kirk, 2014). Species with rapid locomotion, especially predators that rely on sight for prey detection and capture, have larger eyes and higher acuity (Hall et al., 2012). RF size is an important component of pattern vision and object localization, which are arguably more important to survival of prey species than binocular segregation, especially in animals such as rodents that do not have extensive binocular vision (Antonini et al., 1999). Animals with more complex visual behavior, larger visual cortices, and frontally-placed eyes are more likely to have multiple visual representation in cerebral cortex as well as organized submodality representations, such as orientation pinwheels, color blobs, motion tuning modules, ocular dominance columns, etc. (Livingstone and Hubel, 1988; Krubitzer, 2007b; Campi and Krubitzer, 2010; Kaas, 2012; Pallas and Mao, 2012). The collective evidence thus points to strong selective pressure for high-resolution vision in some species, as evidenced in a profound way by these cortical specializations. It is important to examine the role of ecological niche on inter-specific variations in the role of visual experience in receptive field refinement and spatial frequency threshold.

VARIATIONS ON A COMMON THEME?

Visual behavior and the extent to which animals use visual cues in their behavioral repertoires vary considerably across phyla. Yet most of our knowledge about the functioning of visual pathways comes from species that were selected for their tractability as experimental subjects or for convenience. Early studies of retinal circuitry were initially performed in a wide variety of species, for example salamanders (Werblin and Dowling, 1969), frogs (Barlow, 1953; Lettvin et al., 1959), rabbits (Barlow and Levick, 1965), fish (Witkovsky and Dowling, 1969), and horseshoe crabs (Ratliff and Hartline, 1959) in addition to cats (Kuffler, 1953; Enroth-Cugell and Robson, 1966). David Hubel and Torsten Wiesel used cats and macaque monkeys in their pioneering investigations of developing and adult retinogeniculocortical pathways. These species were chosen with the assumption that what was discovered would be relevant to visual pathway function in infant and adult humans. Since then, there has been an almost wholesale shift toward mice as a model organism for studies of visual system development and plasticity, primarily for the ease of using genetic tools. This has occurred without a full consideration of the behavioral and physiological ecology of mice and possible implications for their visual system organization. Ecological niche is likely to have an important effect on not only the structure and function of the visual pathway in adults, but also on the role of vision in its development. For example, nocturnal, fossorial mammals like mice may depend less on visual experience for visual pathway development than diurnal, cursorial species like primates. This is an important consideration for choosing a model organism for studies of visual system development and plasticity. Furthermore, now that it is becoming easier to manipulate gene expression in a variety of species, mice may lose one reason for their popularity.

EVIDENCE THAT THE ROLE OF SENSORY EXPERIENCE IN DEVELOPMENT OF VISUAL RECEPTIVE FIELD PROPERTIES DIFFERS BETWEEN SPECIES AND BETWEEN DIFFERENT RECEPTIVE FIELD PROPERTIES

The concept of a critical period is firmly embedded in the literature, yet is used in different ways by different investigators. Most use the term to mean an early period of development during which the brain can be modified by the environment, with the implication that after the critical period closes, modification is no longer possible. Some prefer the term "sensitive period" to indicate those developmental events that have a decreased sensitivity to external influence with age, but which can still exhibit some level of experience-dependent modification; that is they are more sensitive to extrinsic influence during a certain time period. Language learning is a good example. It is increasingly becoming apparent, however, that one species critical period is another species sensitive period, making it important to carefully consider which term is used and for what circumstances. As mentioned above, mice can exhibit ocular dominance plasticity as adults, but cats cannot. Does this mean that cats have a critical period but mice have a sensitive period for ocular dominance plasticity? Or that we do not yet know how to demonstrate plasticity in adult cats? The evidence that exercise (Kaneko and Stryker, 2014; Kaneko et al., 2017) and environmental enrichment (Greifzu et al., 2014, 2016) can influence plasticity supports this idea.

The timing of the critical period for ocular dominance plasticity is such that it opens soon after the eyes open and vision becomes possible (Berardi et al., 2000). After it closes, visual acuity does not improve substantially, but whether the potential for ocular dominance plasticity makes increased acuity possible seems unlikely, given that acuity increases in both binocular and non-binocular regions of the visual field. The brain and body size and the evolutionary history of a species is a good predictor of the time course of its brain development (Clancy et al., 2001; Workman et al., 2013), including the time course of its critical/sensitive periods (Berardi et al., 2000). If the same mechanism underlies the opening and closing of these periods across species, then all elements of that mechanism, such as BDNF and its receptor (Huang et al., 1999 and in preparation; Mudd et al., in press), must be in place and operational for different periods of time in different species. In cases, where there are differently timed critical periods for different events within a species, this would also be expected.

Examples of species or regional differences in the relationship between visual experience and development of visual circuitry abound. In mouse retinal ganglion cells, spatiotemporal response properties, and contrast detection thresholds do not require vision for their development, but ON and OFF responses do (Ko et al., 2013; Akimov and Rentería, 2014). Direction selectivity in V1 requires visual experience for even rudimentary development in ferret V1 (Li et al., 2006). It can be modified by experience in cats (Berman and Daw, 1977; Leventhal and Hirsch, 1980) and rats (Fagiolini et al., 1994) but not in mice (Rochefort et al., 2011). Mice, but not rats or cats, exhibit ocular dominance plasticity in adulthood, perhaps because of a different mechanism, or perhaps because in larger animals, adult axons have greater distances to bridge to make new connections (Laing et al., 2015). Dark-rearing has only a modest effect on perceptual (Prusky and Douglas, 2003) and physiological (Kang et al., 2013) acuity in mice, but severely reduces spatial resolution of the X-cell form vision pathway in rat (Fagiolini et al., 1994) and cat visual cortex (Timney et al., 1978; Derrington and Hawken, 1981). Spatial frequency selectivity increases independently of visual experience for up to 3 weeks post-natally in cats, but requires visual experience to improve further (Derrington and Fuchs, 1981; Derrington, 1984). Sensitivity to binocular disparity, a measure of depth perception, increases from birth but does not develop during binocular eyelid suture in cats (Pettigrew, 1974). These various pieces of evidence suggest that species differences in the effects of visual deprivation on development of RF properties do exist, and that even within a species, some RF properties require visual experience and some do not. However, there has been little if any attempt to relate these differences to behavioral ecology or to provide a comprehensive investigation. Thus, comparative studies are essential.

VISUAL PATHWAY ORGANIZATION DIFFERS BETWEEN SPECIES

Reflecting differences in visual behavior, species also differ markedly in the number and size of visual regions in the brain, and particularly visual cortical areas (Krubitzer, 2007a; Larsen and Krubitzer, 2008; Campi and Krubitzer, 2010). In general, the number and relative size of areas increases across time in mammalian orders, from rodents to carnivores to primates, for example, but within the very large and diverse Order Rodentia, the area devoted to visual cortex correlates with the importance of vision to behavior (Campi and Krubitzer, 2010). Retinal structure and function also varies (Huberman and Niell, 2011). Most rodents have Y/W-ganglion cell-dominated retinae and emphasize the retinocollicular "where" pathway over the X-dominated, retinogeniculocortical "what" pathway that is more dominant in carnivores and primates (Sherman and Spear, 1982; Livingstone and Hubel, 1987; Henderson et al., 1988; Waleszczyk et al., 2004; Li et al., 2015). This difference in specialization of the retinofugal cells is reflected throughout the visual pathway, in the organization of the retina in terms of differences in density and cellular composition from center to periphery, in the presence or absence of eye- and function-specific modules, and in the number of specialized visual cortical areas. Evolution of a nocturnal habit may have required visual adaptations with broad implications (Smale et al., 2003; Ankel-Simons and Rasmussen, 2008). These differences allow categorization into different groups, with rodents likely having different needs for malleability vs. stability of their visual pathways than carnivores or primates. Our current understanding of critical period regulation thus may not fit a variety of species across visual pathway levels. Thus, more attention needs to be paid to the goal of developing an integrated view of visual system development and evolution in mammals.

SUMMARY

Generation of comparative data is needed to guide *choice of animal models* for visual development studies. Identification of interspecies variations will challenge the *generalizability of mechanistic principles* derived from previous studies of visual development, with the potential to *revise current thinking*. Determining the mechanisms leading to species differences will *provide an answer to the fundamentally important question* of how response properties evolved to match sensory ecology.

AUTHOR CONTRIBUTIONS

SP wrote the manuscript, based on work done in the author's laboratory as well as work done in other laboratories around the world.

FUNDING

Part of the work reviewed in this article was supported by grants awarded to SP by NIH, NSF, the Whitehall Foundation, and Fight for Sight. In addition, SP received internal seed grants from the Brains and Behavior Program, the Molecular Basis of Disease Program, and the Center for Behavioral Neuroscience at Georgia State University.

REFERENCES

Akimov, N. P., and Rentería, R. C. (2014). Dark rearing alters the normal development of spatiotemporal response properties but not of contrast detection threshold in mouse retinal ganglion cells. *Dev. Neurobiol.* 74, 692–706. doi: 10.1002/dneu.22164

Allman, J., Miezin, F., and McGuinness, E. (1985). Stimulus specific responses from beyond the classical receptive field: neurophysiological mechanisms for local-global comparisons in visual neurons. *Annu. Rev. Neurosci.* 8, 407–430. doi: 10.1146/annurev.ne.08.030185.002203

Ankel-Simons, F., and Rasmussen, D. T. (2008). Diurnality, nocturnality, and the evolution of primate visual systems. *Am. J. Phys. Anthropol. Suppl.* 47, 100–117. doi: 10.1002/ajpa.20957

Antonini, A., Fagiolini, M., and Stryker, M. P. (1999). Anatomical correlates of functional plasticity in mouse visual cortex. *J. Neurosci.* 19, 4388–4406.

Arroyo, D. A., and Feller, M. B. (2016). Spatiotemporal features of retinal waves instruct the wiring of the visual circuitry. *Front. Neural Circ.* 10:54. doi: 10.3389/fncir.2016.00054

Artola, A., and Singer, W. (1987). Long-term potentiation and NMDA receptors in rat visual cortex. *Nature* 330, 649–652. doi: 10.1038/330649a0

Balmer, T. S., and Pallas, S. L. (2015a). Refinement but not maintenance of visual receptive fields is independent of visual experience. *Cereb. Cortex* 25, 904–917. doi: 10.1093/cercor/bht281

Balmer, T. S., and Pallas, S. L. (2015b). Visual experience prevents dysregulation of GABAB receptor-dependent short-term depression in adult superior colliculus. *J. Neurophysiol.* 113, 2049–2061. doi: 10.1152/jn.00882.2014

Barlow, H. B. (1953). Summation and inhibition in the frog's retina. *J. Physiol. (Lond).* 119, 69–88. doi: 10.1113/jphysiol.1953.sp004829

Barlow, H. B., and Levick, W. R. (1965). The mechanism of directionally selective units in rabbit's retina. *J. Physiol.* 78, 477–450. doi: 10.1113/jphysiol.1965.sp007638

Bavelier, D., and Neville, H. J. (2002). Cross-modal plasticity: where and how? *Nat. Rev. Neurosci.* 3, 443–452. doi: 10.1038/nrn848

Bavelier, D., Levi, D. M., Li, R. W., Dan, Y., and Hensch, T. K. (2010). Removing brakes on adult brain plasticity: from molecular to behavioral interventions. *J. Neurosci.* 30, 14964–14971. doi: 10.1523/JNEUROSCI.4812-10.2010

Bei, F., Lee, H. H., Liu, X., Gunner, G., Jin, H., Ma, L., et al. (2016). Restoration of visual function by enhancing conduction in regenerated axons. *Cell* 164, 219–232. doi: 10.1016/j.cell.2015.11.036

Berardi, N., Pizzorusso, T., and Maffei, L. (2000). Critical periods during sensory development. *Curr. Opin. Neurobiol.* 10:138. doi: 10.1016/S0959-4388(99)00047-1

Berman, N., and Daw, N. W. (1977). Comparison of the critical periods for monocular and directional deprivation in cats. *J. Physiol.* 265, 249–259. doi: 10.1113/jphysiol.1977.sp011715

Beurdeley, M., Spatazza, J., Lee, H. H. C., Sugiyama, S., Bernard, C., Di Nardo, A. A., et al. (2012). Otx2 Binding to perineuronal nets persistently regulates plasticity in the mature visual cortex. *J. Neurosci.* 32, 9429–9437. doi: 10.1523/JNEUROSCI.0394-12.2012

Blakemore, C. (1990). "Maturation of mechanisms for efficient spatial vision," in *Vision: Coding and Efficiency*, ed C. Blakemore (Cambridge, UK: Cambridge University Press), 254–266.

Bleckert, A., Schwartz, G. W., Turner, M. H., Rieke, F., and Wong, R. O. (2014). Visual space is represented by nonmatching topographies of distinct mouse retinal ganglion cell types. *Curr. Biol.* 24, 310–315. doi: 10.1016/j.cub.2013.12.020

Bloodgood, B. L., Sharma, N., Browne, H. A., Trepman, A. Z., and Greenberg, M. E. (2013). The activity-dependent transcription factor NPAS4 regulates domain-specific inhibition. *Nature* 503, 121–125. doi: 10.1038/nature12743

Bronchti, G., Heil, P., Sadka, R., Hess, A., Scheich, H., and Wollberg, Z. (2002). Auditory activation of "visual" cortical areas in the blind mole rat (*Spalax ehrenbergi*). *J. Comp. Neurol.* 16, 311–329. doi: 10.1046/j.1460-9568.2002.02063.x

Buss, R. R., Sun, W., and Oppenheim, R. W. (2006). Adaptive roles of programmed cell death during nervous system development. *Annu. Rev. Neurosci.* 29, 1–35. doi: 10.1146/annurev.neuro.29.051605.112800

Butler, B. E., Chabot, N., Kral, A., and Lomber, S. G. (2017). Origins of thalamic and cortical projections to the posterior auditory field in congenitally deaf cats. *Hear. Res.* 343, 118–127. doi: 10.1016/j.heares.2016.06.003

Campi, K. L., and Krubitzer, L. (2010). Comparative studies of diurnal and nocturnal rodents: differences in lifestyle result in alterations in cortical field size and number. *J. Comp. Neurol.* 518, 4491–4512. doi: 10.1002/cne.22466

Cang, J., Kaneko, M., Yamada, J., Woods, G., Stryker, M. P., and Feldheim, D. A. (2005). Ephrin-As guide the formation of functional maps in the visual cortex. *Neuron* 48, 577–589. doi: 10.1016/j.neuron.2005.10.026

Carrasco, M. M., and Pallas, S. L. (2006). Early visual experience prevents but cannot reverse deprivation-induced loss of refinement in adult superior colliculus. *Vis. Neurosci.* 23, 845–852. doi: 10.1017/S0952523806230177

Carrasco, M. M., Mao, Y. T., Balmer, T. S., and Pallas, S. L. (2011). Inhibitory plasticity underlies visual deprivation-induced loss of receptive field refinement in the adult superior colliculus. *Eur. J. Neurosci.* 33, 58–68. doi: 10.1111/j.1460-9568.2010.07478.x

Carrasco, M. M., Razak, K. A., and Pallas, S. L. (2005). Visual experience is necessary for maintenance but not development of receptive fields in superior colliculus. *J. Neurophysiol.* 94, 1962–1970. doi: 10.1152/jn.00166.2005

Castillo, P. E., Chiu, C. Q., and Carroll, R. C. (2011). Long-term plasticity at inhibitory synapses. *Curr. Opin. Neurobiol.* 21, 328–338. doi: 10.1016/j.conb.2011.01.006

Chiu, C., and Weliky, M. (2001). Spontaneous activity in developing ferret visual cortex *in vivo*. *J. Neurosci.* 21, 8906–8914.

Clancy, B., Darlington, R. B., and Finlay, B. L. (2001). Translating developmental time across species. *Neuroscience* 105, 7–17. doi: 10.1016/S0306-4522(01)00171-3

Clancy, B., Kersh, B., Hyde, J., Darlington, R. B., Anand, K. J., and Finlay, B. L. (2007). Web-based method for translating neurodevelopment from laboratory species to humans. *Neuroinformatics* 5, 79–94. doi: 10.1385/NI:5:1:79

Cline, H. T., and Constantine-Paton, M. (1989). NMDA receptor antagonists disrupt the retinotectal topographic map. *Neuron* 3, 413–426. doi: 10.1016/0896-6273(89)90201-8

Constantine-Paton, M., and Cline, H. T. (1998). LTP and activity-dependent synaptogenesis: the more alike they are, the more different they become. *Curr. Opin. Neurobiol.* 8, 139–148. doi: 10.1016/S0959-4388(98)80017-2

Debski, E. A., Cline, H. T., and Constantine-Paton, M. (1990). Activity-dependent tuning and the NMDA receptor. *J. Neurobiol.* 21, 18–32. doi: 10.1002/neu.480210103

Derrington, A. M. (1984). Development of spatial frequency selectivity in striate cortex of vision-deprived cats. *Exp. Brain Res.* 55, 431–437. doi: 10.1007/BF00235273

Derrington, A. M., and Fuchs, A. F. (1981). The development of spatial-frequency selectivity in kitten striate cortex. *J. Physiol.* 316, 1–10. doi: 10.1113/jphysiol.1981.sp013767

Derrington, A. M., and Hawken, M. J. (1981). Spatial and temporal properties of cat geniculate neurones after prolonged deprivation. *J. Physiol.* 314, 107–120. doi: 10.1113/jphysiol.1981.sp013694

Ellsworth, C. A., Lyckman, A. W., Feldheim, D. A., Flanagan, J. G., and Sur, M. (2005). Ephrin-A2 and -A5 influence patterning of normal and novel retinal projections to the thalamus: conserved mapping mechanisms in visual and auditory thalamic targets. *J. Comp. Neurol.* 488, 140–151. doi: 10.1002/cne.20602

Enroth-Cugell, C., and Robson, J. G. (1966). The contrast sensitivity of retinal ganglion cells of the cat. *J. Physiol.* 187, 517–552.

Espinosa, J. S., and Stryker, M. P. (2012). Development and plasticity of the primary visual cortex. *Neuron* 75, 230–249. doi: 10.1016/j.neuron.2012.06.009

Fagiolini, M., and Hensch, T. K. (2000). Inhibitory threshold for critical-period activation in primary visual cortex. *Nature* 404, 183–186. doi: 10.1038/35004582

Fagiolini, M., Pizzorusso, T., Berardi, N., Domenici, L., and Maffei, L. (1994). Functional postnatal development of the rat primary visual cortex and the role of visual experience: dark rearing and monocular deprivation. *Vis. Res.* 34, 709–720. doi: 10.1016/0042-6989(94)90210-0

Feldheim, D. A., Kim, Y. I., Bergemann, A. D., Frisén, J., Barbacid, M., and Flanagan, J. G. (2000). Genetic analysis of ephrin-A2 and ephrin-A5 shows their requirement in multiple aspects of retinocollicular mapping. *Neuron* 25, 563–574. doi: 10.1016/S0896-6273(00)81060-0

Feldheim, D. A., Nakamoto, M., Osterfield, M., Gale, N. W., DeChiara, T. M., Rohatgi, R., et al. (2004). Loss-of-function analysis of EphA receptors in retinotectal mapping. *J. Neurosci.* 24, 2542–2550. doi: 10.1523/JNEUROSCI.0239-03.2004

Feller, M. B. (2002). The role of nAChR-mediated spontaneous retinal activity in visual system development. *J. Neurobiol.* 53, 556–567. doi: 10.1002/neu.10140

Finlay, B. L., and Pallas, S. L. (1989). Control of cell number in the developing mammalian visual system. *Prog. Neurobiol.* 32, 207–234. doi: 10.1016/0301-0082(89)90017-8

Finlay, B. L., Schneps, S. E., and Schneider, G. E. (1979). Orderly compression of the retinotectal projection following partial tectal ablations in the newborn hamster. *Nature* 280, 153–154. doi: 10.1038/280153a0

Frost, D. O. (1982). Anomalous visual connections to somatosensory and auditory systems following brain lesions in early life. *Dev. Brain Res.* 3, 627–635. doi: 10.1016/0165-3806(82)90058-X

Gao, W. J., and Pallas, S. L. (1999). Cross-modal reorganization of horizontal connectivity in auditory cortex without altering thalamocortical projections. *J. Neurosci.* 19, 7940–7950.

Glick, H., and Sharma, A. (2017). Cross-modal plasticity in developmental and age-related hearing loss: clinical implications. *Hear. Res.* 343, 191–201. doi: 10.1016/j.heares.2016.08.012

Greifzu, F., Kalogeraki, E., and Lowel, S. (2016). Environmental enrichment preserved lifelong ocular dominance plasticity, but did not improve visual abilities. *Neurobiol. Aging* 41, 130–137. doi: 10.1016/j.neurobiolaging.2016.02.014

Greifzu, F., Pielecka-Fortuna, J., Kalogeraki, E., Krempler, K., Favaro, P. D., Schlüter, O. M., et al. (2014). Environmental enrichment extends ocular dominance plasticity into adulthood and protects from stroke-induced impairments of plasticity. *Proc. Natl. Acad. Sci.* 111, 1150–1155. doi: 10.1073/pnas.1313385111

Gu, Y., Tran, T., Murase, S., Borrell, A., Kirkwood, A., and Quinlan, E. M. (2016). Neuregulin-dependent regulation of fast-spiking interneuron excitability controls the timing of the critical period. *J. Neurosci.* 36, 10285–10295. doi: 10.1523/JNEUROSCI.4242-15.2016

Hall, M. I., Kamilar, J., and Kirk, E. C. (2012). Eye shape and the nocturnal bottleneck of mammals. *Proc. R. Soc. Lond. B* 279, 4962–4968. doi: 10.1098/rspb.2012.2258

Hamburger, V., and Levi-Montalcini, R. (1949). Proliferation, differentiation and degeneration in the spinal ganglia of the chick embryo under normal and experimental conditions. *J. Exp. Zool.* 111, 457–502. doi: 10.1002/jez.1401110308

Hebb, D. O. (1949). *The Organization of Behavior*. New York, NY: John Wiley.

Heil, P., Bronchti, G., Wollberg, Z., and Scheich, H. (1991). Invasion of visual cortex by the auditory system in the naturally blind mole rat. *Neuroreport* 2, 735–738. doi: 10.1097/00001756-199112000-00001

Henderson, Z., Finlay, B. L., and Wikler, K. C. (1988). Development of ganglion cell topography in ferret retina. *J. Neurosci.* 8, 1194–1205.

Hensch, T., Fagiolini, M., Mataga, N., Stryker, M., Baekkeskov, S., and Kash, S. (1998). Local GABA circuit control of experience-dependent plasticity in developing visual cortex. *Science* 282, 1504–1508. doi: 10.1126/science.282.5393.1504

Hinaux, H., Devos, L., Blin, M., Elipot, Y., Bibliowicz, J., Alie, A., et al. (2016). Sensory evolution in blind cavefish is driven by early embryonic events during gastrulation and neurulation. *Development* 143, 4521–4532. doi: 10.1242/dev.141291

Hollyday, M., and Hamburger, V. (1976). Reduction of the naturally occurring motor neuron loss by enlargement of the periphery. *J. Comp. Neurol.* 170, 311–320. doi: 10.1002/cne.901700304

Hong, E. J., McCord, A. E., and Greenberg, M. E. (2008). A biological function for the neuronal activity-dependent component of BDNF transcription in the development of cortical inhibition. *Neuron* 60, 610–624. doi: 10.1016/j.neuron.2008.09.024

Huang, L., and Pallas, S. L. (2001). NMDA antagonists in the superior colliculus prevent developmental plasticity but not visual transmission or map compression. *J. Neurophysiol.* 86, 1179–1194.

Huang, X., Stodieck, S. K., Goetze, B., Cui, L., Wong, M. H., Wenzel, C., et al. (2015). Progressive maturation of silent synapses governs the duration of a critical period. *Proc. Natl. Acad. Sci. U.S.A.* 112, E3131–E3140. doi: 10.1073/pnas.1506488112

Huang, Z. J., Kirkwood, A., and Tonegawa, S. (1999). BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell* 98, 739–755. doi: 10.1016/S0092-8674(00)81509-3

Hübener, M., and Bonhoeffer, T. (2014). Neuronal plasticity: beyond the critical period. *Cell* 159, 727–737. doi: 10.1016/j.cell.2014.10.035

Huberman, A. D., and Niell, C. M. (2011). What can mice tell us about how vision works? *Trends Neurosci.* 34, 464–473. doi: 10.1016/j.tins.2011.07.002

Iwai, Y., Fagiolini, M., Obata, K., and Hensch, T. K. (2003). Rapid critical period induction by tonic inhibition in visual cortex. *J. Neurosci.* 23, 6695–6702.

Jiang, B., Huang, Z. J., Morales, B., and Kirkwood, A. (2005). Maturation of GABAergic transmission and the timing of plasticity in visual cortex. *Brain Res. Rev.* 50, 126–133. doi: 10.1016/j.brainresrev.2005.05.007

Jones, E. G., and Hendry, S. H. C. (1984). "Basket cells," in *Cerebral Cortex*, eds A. Peters and E. G. Jones (New York, NY: Plenum Press), 309–336. doi: 10.1007/978-1-4615-6610-6

Kaas, J. H. (2012). Evolution of columns, modules, and domains in the neocortex of primates. *Proc. Natl. Acad. Sci.* 109(Suppl. 1), 10655–10660. doi: 10.1073/pnas.1201892109

Kaneko, M., and Stryker, M. P. (2014). Sensory experience during locomotion promotes recovery of function in adult visual cortex. *eLife* 3:e02798. doi: 10.7554/eLife.02798

Kaneko, M., Fu, Y., and Stryker, M. P. (2017). Locomotion Induces Stimulus-Specific Response Enhancement in Adult Visual Cortex. *J. Neurosci.* 37, 3532–3543. doi: 10.1523/JNEUROSCI.3760-16.2017

Kang, E., Durand, S., LeBlanc, J. J., Hensch, T. K., Chen, C., and Fagiolini, M. (2013). Visual acuity development and plasticity in the absence of sensory experience. *J. Neurosci.* 33, 17789–17796. doi: 10.1523/JNEUROSCI.1500-13.2013

Kaskan, P. M., Franco, E. C., Yamada, E. S., Silveira, L. C., Darlington, R. B., and Finlay, B. L. (2005). Peripheral variability and central constancy in mammalian visual system evolution. *Proc. Biol. Sci. R. Soc.* 272, 91–100. doi: 10.1098/rspb.2004.2925

Kirkby, L. A., Sack, G. S., Firl, A., and Feller, M. B. (2013). A role for correlated spontaneous activity in the assembly of neural circuits. *Neuron* 80, 1129–1144. doi: 10.1016/j.neuron.2013.10.030

Kirkwood, A., Lee, H.-Y., and Bear, M. F. (1995). Co-regulation of long-term potentiation and experience-dependent synaptic plasticity in visual cortex by age and experience. *Nature* 375, 328–331. doi: 10.1038/375328a0

Ko, H., Cossell, L., Baragli, C., Antolik, J., Clopath, C., Hofer, S. B., et al. (2013). The emergence of functional microcircuits in visual cortex. *Nature* 496, 96–100. doi: 10.1038/nature12015

Kral, A., and Pallas, S. L. (2011). "Development of the auditory cortex," in *The Auditory Cortex*, eds J. A. Winer and C. E. Schreiner (New York, NY: Springer-Verlag), 443–464.

Kral, A., Yusuf, P. A., and Land, R. (2017). Higher-order auditory areas in congenital deafness: top-down interactions and corticocortical decoupling. *Hear. Res.* 343, 50–63. doi: 10.1016/j.heares.2016.08.017

Krubitzer, L. (2007a). The magnificent compromise: cortical field evolution in mammals. *Neuron* 56, 201–208. doi: 10.1016/j.neuron.2007.10.002

Krubitzer, L. A. (2007b). "Captured in the net of space and time: understanding cortical field evolution," in *Evolution of Nervous Systems: Mammals*, eds J. H. Kaas and L. A. Krubitzer (Oxford: Academic Press), 554.

Kuffler, S. W. (1953). Discharge patterns and functional organization of mammalian retina. *J. Neurophysiol.* 16, 37–68.

Kuhlman, S. J., Olivas, N. D., Tring, E., Ikrar, T., Xu, X., and Trachtenberg, J. T. (2013). A disinhibitory microcircuit initiates critical-period plasticity in the visual cortex. *Nature* 501, 543–546. doi: 10.1038/nature12485

Laing, R. J., Turecek, J., Takahata, T., and Olavarria, J. F. (2015). Identification of eye-specific domains and their relation to callosal connections in primary visual cortex of long evans rats. *Cereb. Cortex* 25, 3314–3329. doi: 10.1093/cercor/bhu128

Larsen, D. D., and Krubitzer, L. (2008). Genetic and epigenetic contributions to the cortical phenotype in mammals. *Brain Res. Bull.* 75, 391–397. doi: 10.1016/j.brainresbull.2007.10.041

Law, M. I., and Constantine-Paton, M. (1981). Anatomy and physiology of experimentally produced striped tecta. *J. Neurosci.* 1, 741–759.

Lettvin, J. Y., Maturana, H. R., McCulloch, W. S., and Pitts, W. H. (1959). What the frog's eye tells the frog's brain. *Proc. Inst. Radio Eng.* 47, 1940–1951. doi: 10.1109/jrproc.1959.287207

LeVay, S., Stryker, M. P., and Shatz, C. J. (1978). Ocular dominance columns and their development in layer IV of the cat's visual cortex: a quantitative study. *J. Comp. Neurol.* 179, 223–244. doi: 10.1002/cne.901790113

LeVay, S., Wiesel, T. N., and Hubel, D. H. (1980). The development of ocular dominance columns in normal and visually deprived monkeys. *J. Comp. Neurol.* 191, 1. doi: 10.1002/cne.901910102

Leventhal, A. G., and Hirsch, H. V. (1980). Receptive-field properties of different classes of neurons in visual cortex of normal and dark-reared cats. *J. Neurophysiol.* 43, 1111–1132.

Levitt, J. B., Schumer, R. A., Sherman, S. M., Spear, P. D., and Movshon, J. A. (2001). Visual response properties of neurons in the LGN of normally reared and visually deprived macaque monkeys. *J. Neurophysiol.* 85, 2111–2129.

Li, X., Sun, C., and Shi, L. (2015). Comparison of visual receptive field properties of the superior colliculus and primary visual cortex in rats. *Brain Res. Bull.* 117, 69–80. doi: 10.1016/j.brainresbull.2015.07.007

Li, Y., Fitzpatrick, D., and White, L. E. (2006). The development of direction selectivity in ferret visual cortex requires early visual experience. *Nat. Neurosci.* 9, 676–681. doi: 10.1038/nn1684

Liao, D., Scannevin, R. H., and Huganir, R. (2001). Activation of silent synapses by rapid activity-dependent synaptic recruitment of AMPA receptors. *J. Neurosci.* 21, 6008–6017.

Lim, J. H., Stafford, B. K., Nguyen, P. L., Lien, B. V., Wang, C., Zukor, K., et al. (2016). Neural activity promotes long-distance, target-specific regeneration of adult retinal axons. *Nat. Neurosci.* 19, 1073–1084. doi: 10.1038/nn.4340

Lin, Y., Bloodgood, B. L., Hauser, J. L., Lapan, A. D., Koon, A. C., Kim, T. K., et al. (2008). Activity-dependent regulation of inhibitory synapse development by Npas4. *Nature* 455, 1198–1204. doi: 10.1038/nature07319

Livingstone, M. S., and Hubel, D. H. (1987). Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *J. Neurosci.* 7, 3416–3468.

Livingstone, M., and Hubel, D. H. (1988). Segregation of form, color, movement, and depth: anatomy, physiology, and perception. *Science* 240, 740–749. doi: 10.1126/science.3283936

Lomber, S. G., Meredith, M. A., and Kral, A. (2010). Cross-modal plasticity in specific auditory cortices underlies visual compensations in the deaf. *Nat. Neurosci.* 13, 1421–1427. doi: 10.1038/nn.2653

Lüscher, C., and Malenka, R. C. (2012). NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harb. Perspect. Biol.* 4:a005710. doi: 10.1101/cshperspect.a005710

Mao, Y. T., and Pallas, S. L. (2012). Compromise of auditory cortical tuning and topography after cross-modal invasion by visual inputs. *J. Neurosci.* 32, 10338–10351. doi: 10.1523/JNEUROSCI.6524-11.2012

Mao, Y. T., Cheng, Q., and Pallas, S. L. (2011a). Deletion of ephrin-A interferes with retinocollicular map compression after neonatal target damage [Abstract]. *Soc. Neurosci.* Online Program No. 861.02.

Mao, Y. T., Hua, T. M., and Pallas, S. L. (2011b). Competition and convergence between auditory and cross-modal visual inputs to primary auditory cortical areas. *J. Neurophysiol.* 105, 1558–1573. doi: 10.1152/jn.00407.2010

Mao, Y.-T., and Pallas, S. L. (2013). Cross-modal plasticity results in increased inhibition in primary auditory cortical areas. *Neural Plast.* 2013:18. doi: 10.1155/2013/530651

McLaughlin, T., Torborg, C. L., Feller, M. B., and O'Leary, D. D. (2003). Retinotopic map refinement requires spontaneous retinal waves during a brief critical period of development. *Neuron* 40, 1147–1160. doi: 10.1016/S0896-6273(03)00790-6

Meister, M., Wong, R. O., Baylor, D. A., and Shatz, C. J. (1991). Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina. *Science* 252, 939–943. doi: 10.1126/science.2035024

Middlebrooks, J. C., Dykes, R. W., and Merzenich, M. M. (1980). Binaural response-specific bands in primary auditory cortex (AI) of the cat: topographical organization orthogonal to isofrequency contours. *Brain Res.* 181, 31–48. doi: 10.1016/0006-8993(80)91257-3

Miller, B., Windrem, M. S., and Finlay, B. L. (1991). Thalamic ablations and neocortical development: alterations in thalamic and callosal connectivity. *Cereb. Cortex* 1, 241–261.

Mudd, D. B., Balmer, T. S., and Pallas, S. L. (in press). Early TrkB signaling maintains visual receptive field refinement in adult superior colliculus by preventing a loss of inhibition. *Soc. Neurosci.*

Munz, M., Gobert, D., Schohl, A., Poquerusse, J., Podgorski, K., Spratt, P., et al. (2014). Rapid Hebbian axonal remodeling mediated by visual stimulation. *Science* 344, 904–909. doi: 10.1126/science.1251593

Myers, P., Espinosa, R., Parr, C. S., Jones, T., Hammond, G. S., and Dewey, T. A. (2014). *The Animal Diversity Web.* Available online at: http://animaldiversity.org

Pallas, S. L. (2007). "Compensatory innervation in development and evolution," in *Theories, Development, Invertebrates*, Vol. 1, eds G. F. Striedter and J. L. R. Rubenstein (Oxford: Academic Press), 153–168. doi: 10.1016/b0-12-370878-8/00101-4

Pallas, S. L., and Finlay, B. L. (1989). Conservation of receptive field properties of superior colliculus cells after developmental rearrangements of retinal input. *Vis. Neurosci.* 2, 121–135. doi: 10.1017/S0952523800011986

Pallas, S. L., and Finlay, B. L. (1991). Compensation for population size mismatches in the hamster retinotectal system: alterations in the organization of retinal projections. *Vis. Neurosci.* 6, 271–281. doi: 10.1017/S0952523800006271

Pallas, S. L., and Mao, Y. T. (2012). "The evolution of multisensory neocortex," in *The New Handbook of Multisensory Processes*, ed B. E. Stein (Cambridge, MA: MIT Press), 627–641.

Pallas, S. L., Gilmour, S. M., and Finlay, B. L. (1988). Control of cell number in the developing neocortex. I. Effects of early tectal ablation. *Dev. Brain Res.* 43, 1–11. doi: 10.1016/0165-3806(88)90148-4

Pallas, S. L., Littman, T., and Moore, D. R. (1999). Cross-modal reorganization of callosal connectivity without altering thalamocortical projections. *Proc. Natl. Acad. Sci. U.S.A.* 96, 8751–8756. doi: 10.1073/pnas.96.15.8751

Pallas, S. L., Xu, M., and Razak, K. A. (2006). "Influence of thalamocortical activity on sensory cortical development and plasticity," in *Development and Plasticity in Sensory Thalamus and Cortex*, ed W. G. R. Erzurumlu and Z. Molnar (New York, NY: Kluwer Academic/Plenum Publishers), 120–137. doi: 10.1007/978-0-387-38607-2_8

Park, H., and Poo, M.-M. (2013). Neurotrophin regulation of neural circuit development and function. *Nat. Rev. Neurosci.* 14, 7–23. doi: 10.1038/nrn3379

Parker, A., and Hawken, M. (1985). Capabilities of monkey cortical cells in spatial-resolution tasks. *J. Opt. Soc. Am. A* 2, 1101–1114. doi: 10.1364/JOSAA.2.001101

Peters, A., and Jones, E. G. (1984). *Cerebral Cortex Volume 1: Cellular Components of the Cerebral Cortex*. New York, NY: Plenum Press.

Pettigrew, J. D. (1974). The effect of visual experience on the development of stimulus specificity by kitten cortical neurones. *J. Physiol.* 237, 49–74. doi: 10.1113/jphysiol.1974.sp010469

Philpot, B. D., Sekhar, A. K., Shouval, H. Z., and Bear, M. F. (2001). Visual experience and deprivation bidirectionally modify the composition and function of NMDA receptors in visual cortex. *Neuron* 29, 157–169. doi: 10.1016/S0896-6273(01)00187-8

Prusky, G. T., and Douglas, R. M. (2003). Developmental plasticity of mouse visual acuity. *Eur. J. Neurosci.* 17, 167–173. doi: 10.1046/j.1460-9568.2003.02420.x

Puelles, L., and Rubenstein, J. L. R. (2003). Forebrain gene expression domains and the evolving prosomeric model. *Trends Neurosci.* 26, 469–476. doi: 10.1016/S0166-2236(03)00234-0

Quinlan, E. M., Olstein, D. H., and Bear, M. F. (1999). Bidirectional, experience-dependent regulation of N-methyl-D-aspartate receptor subunit composition in the rat visual cortex during postnatal development. *Proc. Natl. Acad. Sci. U.S.A.* 96, 12876–12880. doi: 10.1073/pnas.96.22.12876

Raabe, J. I., Windrem, M. S., and Finlay, B. L. (1986). Control of cell number in the developing visual system. II. Visual cortical ablation. *Dev. Brain Res.* 28, 1–11. doi: 10.1016/0165-3806(86)90061-1

Ratliff, F., and Hartline, H. K. (1959). The responses of Limulus optic nerve fibers to patterns of illumination on the receptor mosaic. *J. Gen. Physiol.* 42, 1241–1255. doi: 10.1085/jgp.42.6.1241

Rauschecker, J. P., and Korte, M. (1993). Auditory spatial tuning of cortical neurons is sharpened in cats without visual experience. *J. Neurophysiol.* 70, 1717–1721.

Rauschecker, J. P., Tian, B., Korte, M., and Egert, U. (1992). Crossmodal changes in the somatosensory vibrissa/barrel system of visually deprived animals. *Proc. Natl. Acad. Sci. U.S.A.* 89, 5063–5067. doi: 10.1073/pnas.89.11.5063

Razak, K. A., and Pallas, S. L. (2005). Neural mechanisms of stimulus velocity tuning in the superior colliculus. *J. Neurophysiol.* 94, 3573–3589. doi: 10.1152/jn.00816.2004

Razak, K. A., and Pallas, S. L. (2006). Dark rearing reveals the mechanism underlying stimulus size tuning of superior colliculus neurons. *Vis. Neurosci.* 23, 741–748. doi: 10.1017/S0952523806230062

Razak, K. A., and Pallas, S. L. (2007). Inhibitory plasticity facilitates recovery of stimulus velocity tuning in the superior colliculus after chronic NMDA receptor blockade. *J. Neurosci.* 27, 7275–7283. doi: 10.1523/JNEUROSCI.1143-07.2007

Razak, K. A., Fuzessery, Z. M., and Pallas, S. L. (2010). "Developmental plasticity of inhibitory receptive field properties in the auditory and visual systems," in *Developmental Plasticity of Inhibitory Circuitry*, ed S. L. Pallas (New York, NY: Springer), 71–89.

Razak, K. A., Huang, L., and Pallas, S. L. (2003). NMDA receptor blockade in the superior colliculus increases receptive field size without altering velocity and size tuning. *J. Neurophysiol.* 90, 110–119. doi: 10.1152/jn.01029.2002

Rochefort, N. L., Narushima, M., Grienberger, C., Marandi, N., Hill, D. N., and Konnerth, A. (2011). Development of direction selectivity in mouse cortical neurons. *Neuron* 71, 425–432. doi: 10.1016/j.neuron.2011.06.013

Roe, A. W., Pallas, S. L., Hahm, J., and Sur, M. (1990). A map of visual space induced in primary auditory cortex. *Science* 250, 818–820. doi: 10.1126/science.2237432

Roe, A. W., Pallas, S. L., Kwon, Y. H., and Sur, M. (1992). Visual projections routed to the auditory pathway in ferrets: receptive fields of visual neurons in primary auditory cortex. *J. Neurosci.* 12, 3651–3664.

Sanes, D. H., and Kotak, V. C. (2011). Developmental plasticity of auditory cortical inhibitory synapses. *Hear. Res.* 279, 140–148. doi: 10.1016/j.heares.2011.03.015

Sawtell, N. B., Frenkel, M. Y., Philpot, B. D., Nakazawa, K., Tonegawa, S., and Bear, M. F. (2003). NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. *Neuron* 38, 977–985. doi: 10.1016/S0896-6273(03)00323-4

Schmidt, J. T. (1983). Regeneration of the retinotectal projection following compression onto a half tectum in goldfish. *J. Embryol. Exp. Morphol.* 77, 39–51.

Schmidt, J. T., Buzzard, M., Borress, R., and Dhillon, S. (2000). MK801 increases retinotectal arbor size in developing zebrafish without affecting kinetics of branch elimination and addition. *J. Neurobiol.* 42, 303–314. doi: 10.1002/(SICI)1097-4695(20000215)42:3<303::AID-NEU2>3.0.CO;2-A

Schneider, G. E. (1973). Early lesions of the superior colliculus: factors affecting the formation of abnormal retinal projections. *Brain Behav. Evol.* 8, 73–109. doi: 10.1159/000124348

Schormans, A. L., Typlt, M., and Allman, B. L. (2017). Crossmodal plasticity in auditory, visual and multisensory cortical areas following noise-induced hearing loss in adulthood. *Hear. Res.* 343, 92–107. doi: 10.1016/j.heares.2016.06.017

Sherman, S. M., and Spear, P. D. (1982). Organization of visual pathways in normal and visually-deprived cats. *Physiol. Rev.* 62, 738–855.

Smale, L., Lee, T., and Nunez, A. A. (2003). Mammalian diurnality: some facts and gaps. *J. Biol. Rhythms* 18, 356–366. doi: 10.1177/0748730403256651

Spiegel, I., Mardinly, A. R., Gabel, H. W., Bazinet, J. E., Couch, C. H., Tzeng, C. P., et al. (2014). Npas4 regulates excitatory-inhibitory balance within neural circuits through cell-type-specific gene programs. *Cell* 157, 1216–1229. doi: 10.1016/j.cell.2014.03.058

Stent, G. (1973). A physiological mechanism for Hebb's postulate of learning. *Proc. Natl. Acad. Sci. U.S.A.* 70, 997–1001. doi: 10.1073/pnas.70.4.997

Sur, M., Garraghty, P. E., and Roe, A. W. (1988). Experimentally induced visual projections into auditory thalamus and cortex. *Science* 242, 1437–1441. doi: 10.1126/science.2462279

Tadesse, T., Cheng, Q., Xu, M., Baro, D. J., Young, L. J., and Pallas, S. L. (2013). Regulation of ephrin-A expression in compressed retinocollicular maps. *Dev. Neurobiol.* 73, 274–296. doi: 10.1002/dneu.22059

Timney, B., Mitchell, D. E., and Giffin, F. (1978). The development of vision in cats after extended periods of dark-rearing. *Exp. Brain Res.* 31, 547–560. doi: 10.1007/BF00239811

Trachtenberg, J. T. (2015). Competition, inhibition, and critical periods of cortical plasticity. *Curr. Opin. Neurobiol.* 35, 44–48. doi: 10.1016/j.conb.2015.06.006

Troilo, D., Xiong, M. J., Crowley, J. C., and Finlay, B. L. (1996). Factors controlling the dendritic arborization of retinal ganglion cells. *Vis. Neurosci.* 13, 721–733. doi: 10.1017/S0952523800008609

Trusk, T. C., Kaboord, W. S., and Wong-Riley, M. T. T. (1989). Effects of monocular enucleation, tetrodoxin, and lid suture on cytochrome-oxidase reactivity in supragranular puffs of adult macaque striate cortex. *Vis. Neurosci.* 4, 185–204. doi: 10.1017/S0952523800003345

Udin, S. B. (1977). Rearrangements of the retinotectal projection in Rana pipiens after unilateral caudal half-tectum ablation. *J. Comp. Neurol.* 173, 561–582. doi: 10.1002/cne.901730310

Udin, S. B. (2012). Binocular maps in Xenopus tectum: visual experience and the development of isthmotectal topography. *Dev. Neurobiol.* 72, 564–574. doi: 10.1002/dneu.20933

Udin, S. B., and Keating, M. J. (1981). Plasticity in a central nervous pathway in xenopus: anatomical changes in the isthmotectal projection after larval eye rotation. *J. Comp. Neurol.* 203, 575–594. doi: 10.1002/cne.902030403

Van den Bergh, G., Zhang, B., Arckens, L., and Chino, Y. M. (2010). Receptive-field properties of V1 and V2 neurons in mice and macaque monkeys. *J. Comp. Neurol.* 518, 2051–2070. doi: 10.1002/cne.22321

van Versendaal, D., Rajendran, R., Saiepour, M. H., Klooster, J., Smit-Rigter, L., Sommeijer, J.-P., et al. (2012). Elimination of inhibitory synapses Is a major component of adult ocular dominance plasticity. *Neuron* 74, 374–383. doi: 10.1016/j.neuron.2012.03.015

Veilleux, C. C., and Kirk, E. C. (2014). Visual acuity in mammals: effects of eye size and ecology. *Brain Behav. Evol.* 83, 43–53. doi: 10.1159/000357830

Waleszczyk, W. J., Wang, C., Benedek, G., Burke, W., and Dreher, B. (2004). Motion sensitivity in cat's superior colliculus: contribution of different visual processing channels to response properties of collicular neurons. *Acta Neurobiol. Exp.* 64, 209–228.

Wallace, M. T., Carriere, B. N., Perrault, T. J. Jr., Vaughan, J. W., and Stein, B. E. (2006). The development of cortical multisensory integration. *J. Neurosci.* 26, 11844–11849. doi: 10.1523/JNEUROSCI.3295-06.2006

Wallace, M. T., Meredith, M. A., and Stein, B. E. (1992). Integration of multiple sensory modalities in cat cortex. *Exp. Brain Res.* 91, 484–488. doi: 10.1007/BF00227844

Wang, Q., Sporns, O., and Burkhalter, A. (2012). Network analysis of corticocortical connections reveals ventral and dorsal processing streams in mouse visual cortex. *J. Neurosci.* 32, 4386–4399. doi: 10.1523/JNEUROSCI.6063-11.2012

Weliky, M., and Katz, L. C. (1999). Correlational structure of spontaneous neuronal activity in the developing lateral geniculate nucleus *in vivo*. *Science* 285, 599–604. doi: 10.1126/science.285.5427.599

Werblin, F. S., and Dowling, J. E. (1969). Organization of the retina of the mudpuppy, Necturus maculosus. II. Intracellular recording. *J. Neurophysiol.* 32, 339–355.

Wikler, K. C., and Rakic, P. (1996). Development of photoreceptor mosaics in the primate retina. *Perspect. Dev. Neurobiol.* 3, 161–175.

Wikler, K. C., Kirn, J., Windrem, M. S., and Finlay, B. L. (1986). Control of cell number in the developing visual system. II. Effects of partial tectal ablation. *Dev. Brain Res.* 28, 11–21. doi: 10.1016/0165-3806(86)90060-X

Wilson, D. E., and Reeder, D. M. (eds.) (2005). *Mammal Species of the World, a Taxonomic and Geographic Reference*. Baltimore, MD: The Johns Hopkins University Press.

Witkovsky, P., and Dowling, J. E. (1969). Synaptic relationships in the plexiform layers of carp retina. *Z. Zellforsch. Mikrosk. Anat.* 100, 60–82. doi: 10.1007/BF00343821

Wong, R. O. L., Meister, M., and Shatz, C. J. (1993). Transient period of correlated bursting activity during development of the mammalian retina. *Neuron* 11, 923–938. doi: 10.1016/0896-6273(93)90122-8

Woo, T.-U., Niederer, J. K., and Finlay, B. L. (1992). Effect of depletion of layer IV on dorsal lateral geniculate cell number and ingrowth of geniculocortical axons. *Soc. Neurosci. Abs.* 18:777.

Woolsey, T. A., and Van der Loos, H. (1970). The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex. The description of a cortical field composed of discrete cytoarchitectonic units. *Brain Res.* 17, 205–242. doi: 10.1016/0006-8993(70)90079-X

Workman, A. D., Charvet, C. J., Clancy, B., Darlington, R. B., and Finlay, B. L. (2013). Modeling transformations of neurodevelopmental

sequences across mammalian species. *J. Neurosci.* 33, 7368–7383. doi: 10.1523/JNEUROSCI.5746-12.2013

Xiong, M., Pallas, S. L., Lim, S., and Finlay, B. L. (1994). Regulation of retinal ganglion cell axon arbor size by target availability: mechanisms of compression and expansion of the retinotectal projection. *J. Comp. Neurol.* 344, 581–597. doi: 10.1002/cne.903440407

Ypsilanti, A. R., and Rubenstein, J. L. R. (2016). Transcriptional and epigenetic mechanisms of early cortical development: an examination of how Pax6 coordinates cortical development. *J. Comp. Neurol.* 524, 609–629. doi: 10.1002/cne.23866

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

REVIEW
published: 11 August 2015
doi: 10.3389/fnins.2015.00281

Integrating brain, behavior, and phylogeny to understand the evolution of sensory systems in birds

Douglas R. Wylie[1]*, *Cristian Gutiérrez-Ibáñez*[2] and *Andrew N. Iwaniuk*[3]

[1] Neurosciences and Mental Health Institute, University of Alberta, Edmonton, AB, Canada, [2] Lehrstuhl für Zoologie, Technische Universität München, Freising-Weihenstephan, Germany, [3] Department of Neuroscience, University of Lethbridge, Lethbridge, AB, Canada

The comparative anatomy of sensory systems has played a major role in developing theories and principles central to evolutionary neuroscience. This includes the central tenet of many comparative studies, the principle of proper mass, which states that the size of a neural structure reflects its processing capacity. The size of structures within the sensory system is not, however, the only salient variable in sensory evolution. Further, the evolution of the brain and behavior are intimately tied to phylogenetic history, requiring studies to integrate neuroanatomy with behavior and phylogeny to gain a more holistic view of brain evolution. Birds have proven to be a useful group for these studies because of widespread interest in their phylogenetic relationships and a wealth of information on the functional organization of most of their sensory pathways. In this review, we examine the principle of proper mass in relation differences in the sensory capabilities among birds. We discuss how neuroanatomy, behavior, and phylogeny can be integrated to understand the evolution of sensory systems in birds providing evidence from visual, auditory, and somatosensory systems. We also consider the concept of a "trade-off," whereby one sensory system (or subpathway within a sensory system), may be expanded in size, at the expense of others, which are reduced in size.

Keywords: principle of proper mass, wulst, lentiformis mesencephali, isthmo-optic nucleus, somatosensory specializations, prv, brain–behavior relationships, sound localization

OPEN ACCESS

Edited by:
Jorge Mpodozis, Universidad de Chile, Chile

Reviewed by:
Paul Manger, University of the Witwatersrand, South Africa
Juan-Carlos Letelier, Universidad de Chile, Chile

***Correspondence:**
Douglas R. Wylie, Department of Psychology, University of Alberta, Edmonton, AB T6G 2E9, Canada
dwylie@ualberta.ca

Specialty section:
This article was submitted to Evolutionary Psychology and Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *27 April 2015*
Accepted: *28 July 2015*
Published: *11 August 2015*

Citation:
Wylie DR, Gutiérrez-Ibáñez C and Iwaniuk AN (2015) Integrating brain, behavior, and phylogeny to understand the evolution of sensory systems in birds. Front. Neurosci. 9:281. doi: 10.3389/fnins.2015.00281

Introduction

Comparative anatomy of sensory systems has played a major role in developing theories and principles central to evolutionary neuroscience. As a simple example, lateral inhibition was first described in the ommatidia of the horseshoe crab (*Limula* sp.) (Hartline and Ratliff, 1972; Fahrenbach, 1985), but is essential to our understanding of visual processing in mammals and other vertebrates. Modern comparative neuroanatomy often uses multispecies data sets in which attempts are made to understand the evolution of specific behaviors and the correlated evolution of the brain and behavior. The latter studies, comparative studies of brain–behavior relationships, have flourished in recent years as a result of increased interest in understanding how the brain has evolved, (Striedter, 2005) as well as the development of advanced statistical methods to explore evolutionary patterns (Felsenstein, 1985; Harvey and Pagel, 1991; Garland et al., 1993; Pagel, 1999; Revell, 2010). These studies range in scope from analyses of relative brain size in relation to various life history variables and behaviors

(e.g., Iwaniuk et al., 2001, 2004; Lefebvre et al., 2004; Pérez-Barbería et al., 2007; Sol et al., 2007, 2008) to the size of brain regions in relation to specific behaviors (Barton et al., 1995; e.g., Barton, 1998; Pellis and Iwaniuk, 2002; Sherry, 2006; Lindenfors et al., 2007). These kinds of studies have not been exempt of criticism. Healy and Rowe (2007) for example, suggested that correlations between behavioral or ecological factors and relative brain size are meaningless because the brain is composed of multiple, distinct functional units, and therefore changes in the size of the entire brain tell us little about the relationship between brain and behavior. At the same time, these same authors point out that, on the other hand, studies of specific sensory or motor regions, with clear defined function are much more useful as they can point out directly when and where selection is acting upon neural structures.

An inherent assumption of this type of correlational approach to brain–behavior relationships is that larger means better; i.e., that a bigger relative volume results in a better and faster processing of information. This principle is known as the "principle of proper mass" (Jerison, 1973), which states that the size of a neural structure is a reflection of the complexity of the behaviors that it subserves. While Jerison did not explicitly differentiate between absolute and relative size (Striedter, 2005), it is now widely accepted that more complex behavior means a larger relative size and not absolute size (but see Deaner et al., 2007 and Azevedo et al., 2009 for a discussions of the importance of absolute brain size in relation to cognition in mammals). Differences in relative volume of a neural structure are usually thought to reflect an increase in the number of neurons. Even though a positive correlation between volume and cell numbers has only been shown for particular neural structures a few times (Moore et al., 2011; Gutiérrez-Ibáñez et al., 2012), the total brain volume correlates well with the total number of neurons and appears to be one of the main factors that explains differences in relative brain size (Herculano-Houzel et al., 2007; Herculano-Houzel, 2009). Variation in neuronal numbers is not, however, the only factor explaining differences in the relative size of neural structures. For example, in some songbirds, seasonal changes in volume of song control brain nuclei involved in song learning are also associated with changes in neuron soma area (e.g., Tramontin et al., 2000; Thompson and Brenowitz, 2005) and dendritic structure (Hill and DeVoogd, 1991). Thus, differences in relative brain region size can arise from adding neurons or increasing the size of neurons.

Certainly the size of structures within the sensory system is not, however, the only salient variable in the evolution of sensory systems. The evolution of the brain and behavior are intimately tied to the evolutionary history of the species being examined (Harvey and Pagel, 1991; Striedter, 2005; Sherry, 2006). The vast majority of modern comparative studies therefore examine allometry, species differences in relative brain region size and brain–behavior relationships within a phylogenetic context, which enables a more accurate and holistic view of brain evolution (Iwaniuk, 2004; Striedter, 2005). Birds have proven to be a useful group for these studies because of widespread interest in their phylogenetic relationships (Hackett et al., 2008; Jarvis et al., 2014), the diversity of their sensory capabilities, and a wealth of information on the functional organization of most of their sensory pathways (Zeigler and Bischof, 1993; Dubbeldam, 1998; Dooling and Fay, 2000).

In this review, we examine the principle of proper mass in relation differences in the sensory capabilities among birds. We discuss how neuroanatomy, behavior, and phylogeny can be integrated to understand the evolution of sensory systems in birds providing evidence from visual, auditory and somatosensory systems. We also consider the concept of a "trade-off," whereby one sensory system (or subpathway within a sensory system), may be expanded in size, at the expense of others, which are reduced in size.

Visual Systems in Birds

Figure 1 shows a schematic of the visual connections in the avian visual system. The tectofugal pathway would be considered the major visual pathway as the optic tectum (TeO) receives more than 90% of retinal projections (Hunt and Webster, 1975; Remy and Güntürkün, 1991; Mpodozis et al., 1995). The TeO projects to the nucleus rotundus (nRt), which in turn projects to the entopallium (E) in the telencephalon (Benowitz and Karten, 1976; Nixdorf and Bischof, 1982; Miceli and Repérant, 1985; Karten and Shimizu, 1989; Bischof and Watanabe, 1997; Hellmann and Güntürkün, 1999; Laverghetta and Shimizu, 2003; Marín et al., 2003; Hellmann et al., 2004). Collectively, this pathway is involved in many visual behaviors and processes including brightness, color, pattern discrimination, and simple and complex motion (Frost and Nakayama, 1983; Remy and Güntürkün, 1991; Wang et al., 1993; Bischof and Watanabe, 1997; Luksch et al., 1998; Sun and Frost, 1998; Husband and Shimizu, 2001; Nguyen et al., 2004). The TeO is intimately connected with the isthmal nuclei, which includes the magnocellular and parvocellular parts of the nucleus isthmi (Imc and Ipc) and the nucleus semilunaris (SLu) (Hunt and Künzle, 1976; Brecha, 1978; Güntürkün and Remy, 1990; Hellmann and Güntürkün, 2001; Wang et al., 2004, 2006; Tömböl et al., 2006). These nuclei are involved in selective attention (Marín

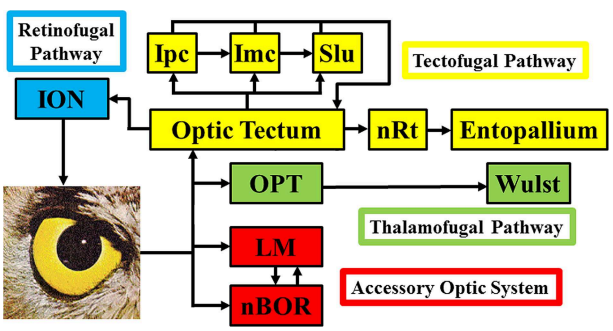


FIGURE 1 | Basic connections of the visual systems in birds. ION, Isthmo-optic nucleus; Ipc/Imc, nucleus isthmi parvocellular/magnocellular; Slu, nucleus semilunaris; nRt, nucleus rotundus; OPT, principal optic nucleus of the thalamus; LM, nucleus lentiformis mesencephalic; nBOR, nucleus of the basal optic root.

et al., 2003, 2007; Marin et al., 2012). The thalamofugal pathway is considered homologous to the geniculo-striate pathway in mammals and includes nuclei within the anterior dorsolateral thalamus collectively known as the principal optic nuclei of the thalamus (OPT), which projects to the visual Wulst (also known as the hyperpallium) (Karten et al., 1973; Karten and Shimizu, 1989; Shimizu and Karten, 1991; Medina and Reiner, 2000; Butler and Hodos, 2005; Reiner et al., 2005). The function of this pathway has been somewhat controversial (Martin, 2009), but it appears to play a role in spatial orientation (Michael et al., 2015), motion perception (Baron et al., 2007), and binocular vision (Pettigrew and Konishi, 1976). The nucleus of the basal optic root (nBOR) and the nucleus lentiformis mesencephalic (LM) are retinal-recipient nuclei (Karten et al., 1977; Reiner et al., 1979; Fite et al., 1981; Gamlin and Cohen, 1988; Wylie et al., 2014) collectively referred to as the Accessory Optic System (AOS) (Simpson, 1984), although technically the LM is a pretectal structure (Giolli et al., 2006). The AOS has a very specific function insofar as it is involved in the analysis of optic flow that results from self-motion and generating the optokinetic response (OKR) (Simpson, 1984; Simpson et al., 1988; Grasse and Cynader, 1990; Gamlin, 2006; Giolli et al., 2006). This is discussed in more detail below. Finally, in **Figure 1** we also show the retinofugal pathway. The isthmo optic nucleus (ION), receives projections from the tectum and sends projections to the retina, thus creating a loop between retina, TeO and ION (Holden, 1968; Weidner et al., 1987; Wolf-Oberhollenzer, 1987). Numerous functions have been proposed for this pathway (for reviews see Repérant et al., 2006; Wilson and Lindstrom, 2011), which we tested through a detailed comparative analysis of ION size (Gutiérrez-Ibáñez et al., 2012).

Hypertrophy of the LM in Hummingbirds

Assuming Jerison's Principle of Proper Mass, and given knowledge of the functions of specific visual pathways combined with knowledge of visual ecology and behavior, one can make predictions of the relative sizes of the visual nuclei in the brain. As mentioned above, the AOS is involved in the analysis of optic flow and the generation of the OKR to mediate retinal image stabilization. Iwaniuk and Wylie (2007) predicted that the nuclei of the AOS would be enlarged in hummingbirds to support their sustained hovering flight, which is unique among birds (Altshuler and Dudley, 2002). Hummingbirds beat their wings up to 50 times faster than other birds (Schuchmann, 1999), produce force during both up and down strokes rather than just up strokes (Warrick et al., 2005). Kinematically, the hovering flight of hummingbirds is unlike that of other birds, but is remarkably similar to that of some insects (Warrick et al., 2005). A critical feature of hovering is stabilization: hummingbirds are able to maintain a stable position in space, despite perturbations that must occur due to the inertia caused by wingbeats, and environmental factors such as wind gusts. Stabilization is controlled by several vestibular, visual, and proprioceptive reflexes, including the OKR (Wilson and Melvill Jones, 1979; for reviews see Ito, 1984; Melvill-Jones, 2000). To reiterate, the OKR is a visual following response to large moving visual stimuli (i.e., optic flow caused by self-motion) whereby eye, head, and body movements are made in the direction of motion to minimize the amount of visual motion across the retina. Lesions to either the nBOR or LM significantly impairs or outright abolishes the OKR (Fite et al., 1981; Gioanni et al., 1983a,b), and neurons in these nuclei have extremely large receptive fields and exhibit direction selectivity to optic flow stimuli (Burns and Wallman, 1981; Morgan and Frost, 1981; Gioanni et al., 1984; Winterson and Brauth, 1985; Frost et al., 1990). Most LM and nBOR neurons prefer extremely slow stimulus velocities on the order of about 1°/s (Burns and Wallman, 1981; Wylie and Crowder, 2000; Crowder et al., 2003) and as such are thought to provide the error signal that drives the OKR (Simpson, 1984; Simpson et al., 1988; Miles and Wallman, 1993). Given this, we hypothesized that both nBOR and LM would be hypertrophied in hummingbirds, compared with other birds, to meet the increased optic flow processing and OKR demands of hovering flight. We found that the LM, but not the nBOR, was significantly larger in hummingbirds compared to other birds (**Figure 2**). When expressed as a percentage of brain volume, the LM in hummingbirds was, on average, more than 3X larger than that of other birds (**Figure 2D**). Thus, we concluded that the OKR is critical for the unique ability of hummingbirds to hover, and this necessitated an increase in the size of the LM, as it is involved in mediating the OKR. This suggestion has recently been confirmed by Goller and Altshuler (2014). They filmed free-flight hummingbirds in a virtual reality environment to examine hovering in the presence of moving patterns. They found that hummingbirds lost positional stability and responded appropriately to the moving stimulus to minimize optic flow.

Binocular Vision and the Wulst

There is considerable variation in the size of the visual Wulst among birds and it appears have become enlarged to support global stereopsis associated with binocular vision (Iwaniuk and Hurd, 2005; Iwaniuk and Wylie, 2006; Iwaniuk et al., 2008). Based upon physiological and hodological evidence, the Wulst is considered the homolog of mammalian primary visual cortex (V1) (Karten et al., 1973; Pettigrew, 1979; Shimizu and Karten, 1993; Medina and Reiner, 2000; Husband and Shimizu, 2001; Reiner et al., 2005). Based on external morphology of the brain, owls appear to have a greatly hypertrophied Wulst compared to other groups of birds (**Figures 3A,C**). In owls, this coincides with a large frontal binocular overlap on the order of 50° (Martin, 1984; Pettigrew and Konishi, 1984; Wylie et al., 1994), which is much greater than that measured in other birds (Katzir and Martin, 1999; Martin and Coetzee, 2004). Electrophysiological studies in owls show that, as in V1, the Wulst is retinotopically organized and neurons are tuned to spatial frequency and orientation. Furthermore, the majority of cells in the Wulst have receptive fields located in the area of binocular overlap. Most cells (about 85%) are binocular, and sensitive to retinal disparity (Pettigrew and Konishi, 1976; Pettigrew, 1978, 1979; Porciatti et al., 1990; Wagner and Frost, 1993; Nieder and Wagner, 2000, 2001). Binocular neurons are present in the Wulst of other species, but they are not as numerous as they are in owls (Pettigrew, 1978; Wilson, 1980; Denton, 1981; Michael et al.,

2015). Together, this suggests that one of the primary functions of the visual Wulst is to mediate binocular vision and/or stereopsis. In support of this hypothesis, Iwaniuk and Wylie (2006) showed that an enlarged visual Wulst seems to have evolved in concert with binocular vision in other nocturnal birds as well. Both the Owlet-Nightjars (genus *Aegotheles*) and frogmouths (genus *Podargus*) are thought to possess stereopsis (Pettigrew, 1986) and have large areas of binocular overlap rivaling that of the owls (Pettigrew and Konishi, 1984; Wallman and Pettigrew, 1985; Martin et al., 2004a). The Wulst is also quite large in these birds, showing a similar degree of hypertrophy as seen in owls (**Figures 3A,B,D**) (Iwaniuk and Wylie, 2006; Iwaniuk et al., 2008), including a prominent pattern of lamination. The closely related nightjars and potoos (genus *Nyctibius*) do not share this Wulst hypertrophy and have a much narrower binocular visual field (Martin et al., 2004a,b).

The relationship between the size of the Wulst and degree of binocular vision seems to hold beyond these birds with a large degree of binocular overlap. Using a data set including 58 different species, Iwaniuk et al. (2008) examined the relationship between the size of the Wulst and binocular vision using orbit orientation as a proxy for binocular overlap (**Figure 3E**). The relative size of the Wulst was significantly correlated with orbit orientation (**Figure 3E**), but relative TeO size was not. Although these multiple lines of evidence indicate that the Wulst is enlarged in species to support binocular vision and global stereopsis, there are some clear exceptions. The oilbird (*Steatornis caripensis*) has a large binocular overlap (Pettigrew and Konishi,

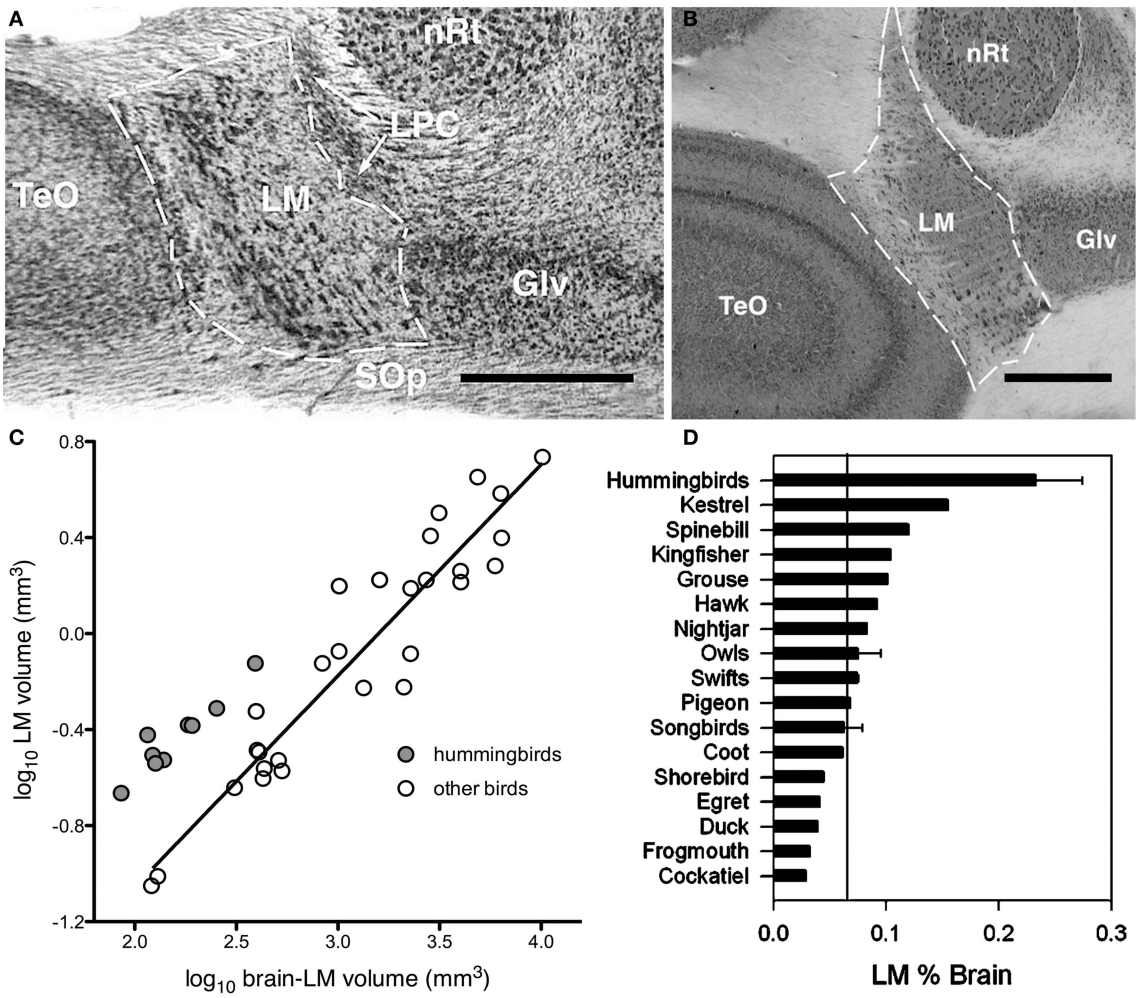


FIGURE 2 | Hypertrophy of the nucleus lentiformis mesencephalic (LM) in hummingbirds. (A,B) Photomicrographs showing the location and borders of LM in coronal sections for a hummingbird (Fork-tailed woodnymph, *Thalurania furcate*) and a songbird (Eastern yellow robin, *Eopsaltria australis*). Although the brain of the songbird is much larger than that of the hummingbird, they share a similar LM volume. **(C)** Shows a scatter plot of the relative size of LM as a function of brain minus LM volume (log transformed). The hummingbirds are indicated by the gray circles and other birds by the white circles. The solid line indicates the least squares linear regression line for all species. **(D)** Bar graph of the relative size of LM expressed as a percentage of total brain volume. The solid line indicates the mean for all non-hummingbirds and the error bars indicate the standard deviations. TeO, optic tectum; LPC, nucleus laminaris precommissuralis; nRt, nucleus rotundus; Glv, lateral geniculate nucleus, ventral leaflet; SOp, stratum opticum. Scale bars = 0.5 mm (adapted from Iwaniuk and Wylie, 2007).

1984) and a hypertrophied Wulst (**Figure 3D**), however, an electrophysiological study failed to find any binocular neurons in the Wulst (Pettigrew and Konishi, 1984). Iwaniuk and Wylie (2006) suggested that binocular vision has been lost in the Oilbird as a consequence of roosting deep within caves and the moderately enlarged Wulst could therefore be a "carryover" from a stereoscopic ancestor. To further complicate this link between relative Wulst size and binocularity, hawks, eagles, and falcons have an abundance of binocular disparity sensitive neurons in the Wulst (Pettigrew, 1978) and stereopsis (Fox et al., 1977), but have a narrow binocular field (Wallman and Pettigrew, 1985; Katzir and Martin, 1999) and a relatively small Wulst (Iwaniuk et al., 2008). Some authors have even suggested that the Wulst has different functions in frontally vs. laterally eyed birds (Michael et al., 2015). Last, it also worth noting that the Wulst is not an exclusively visual structure; the rostral Wulst receives somatosensory projections (Funke, 1989; Wild, 1997; Medina and Reiner, 2000; Manger et al., 2002). In species that forage using tactile information originating in the beak, the rostral Wulst is hypertrophied (Pettigrew and Frost, 1985). One possible explanation for the enlargement of the oilbird's Wulst could therefore be a reflection of increased reliance on somatosensory information from its rictal bristles. This caveat in itself suggests one should be cautious with the general approach to using Jerison's Principle of Proper Mass given that many neural structures can be heterogeneous.

Variation in the Size of the Isthmo-optic Nucleus (ION)

In most studies using Jerison's Principle of Proper Mass, including our studies of the LM (Iwaniuk and Wylie, 2007) and Wulst (Iwaniuk and Wylie, 2006; Iwaniuk et al., 2008) outlined above, the correlation between a structure and a behavior is established with an *a priori* knowledge that the structure is related to the generation of the behavior or sensory modality. Gutiérrez-Ibáñez et al. (2012) examined variation in the size of the ION applying the opposite strategy: the relative size of the structure was used to determine the

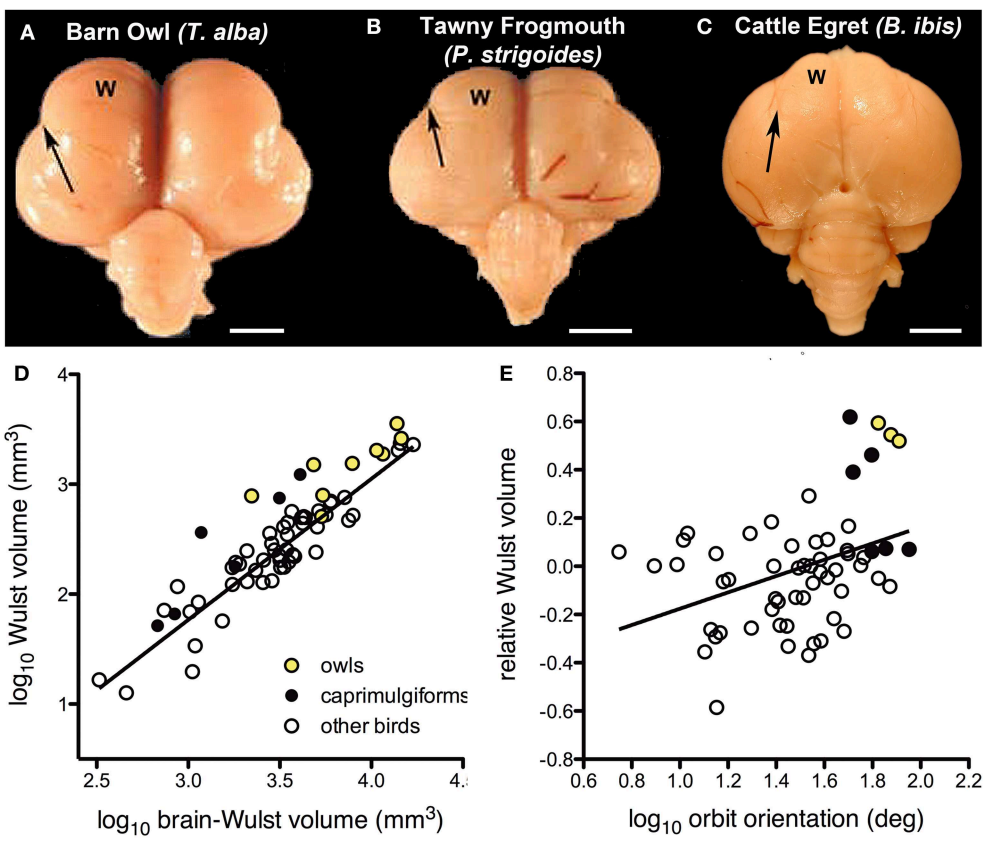


FIGURE 3 | Variation in the size of the visual Wulst (W) is related to binocular vision and stereopsis. (**A**,**B** and **C**) respectively show dorsal views of the Barn Owl *(T. alba)*; Tawny Frogmouth *(P. strigoides)*; and the Cattle Egret *(B. ibis)*. The valecula, the lateral border of the Wulst, is indicated by the arrow. Scale bars = 5 mm. Adapted from Iwaniuk et al. (2006). **(D)** Shows a scatter plot Wulst volume as a function of brain minus Wulst volume. **(E)** Shows a scatterplot of Wulst volume relative to brain volume as a function of orbit orientation. The yellow circles indicate the owls (Strigiformes), black circles indicate Caprimuligiformes and the open circles are other species. The three species of Caprimulgiformes with the largest Wulst are the Oilbird *(S. caripensis)*, the Feline Owlet-nightjar *(A. insignis)*, and the Tawny Frogmouth *(P. strigoides)*. Adapted from Iwaniuk et al. (2008) with additional data from Gutiérrez-Ibáñez et al. (2013).

function of the ION. There have been numerous studies of the ION in birds with little consensus on its function (for reviews see Repérant et al., 2006; Wilson and Lindstrom, 2011). The various functions proposed for the ION include: shifting of visual attention (Rogers and Miles, 1972; Catsicas et al., 1987; Uchiyama, 1989; Ward et al., 1991; Clarke et al., 1996; Uchiyama et al., 1998), saccadic suppression (Holden, 1968; Nickla et al., 1994) enhancement of peripheral vision (Marin et al., 1990), modulation of temporal processing (Knipling, 1978), feeding/pecking (Shortess and Klose, 1977; Weidner et al., 1987; Repérant et al., 1989; Hahmann and Güntürkün, 1992), and detection of aerial predators (Wilson and Lindstrom, 2011).

Gutiérrez-Ibáñez et al. (2012) examined interspecific variation in the relative size of ION in an attempt to address its function. For example, if the ION is an essential component of pecking behavior, then we predicted that species that feed on the ground, such as granivorous finches and galliforms, would have an enlarged ION. Alternatively, if the ION is critical for the detection of aerial predators, then prey species should have larger ION volumes than predatory species. Across 81 species, there was considerable variation in the relative size of the ION (**Figure 4A**). In some birds, including basal, paleognathous species, the ION was not apparent in Nissl stained sections When expressed as a percentage of total brain volume, the ION was quite small in owls and diurnal raptors, but quite large in coots, some shorebirds, songbirds, hummingbirds, woodpeckers, pigeons, and galliforms (**Figure 4B**).

The ION varied not only in size but also the complexity of its visible morphology. The complexity was assigned to one of five categories representing and increasing degree of complexity. For example in category 1, the ION is an evenly distributed mass of cells with somewhat indistinct borders (**Figure 4C**). In category 3, the ION is characterized by a sharper border with a distinct layer of cells that encapsulates the rest of the nucleus (**Figure 4D**). In category 5, all cells appear to be organized into distinct layers with a clearly recognizable neuropil between the layers (**Figure 4E**). Generally speaking, the complexity of the ION was correlated with size, such that birds with a relatively large ION also had a more complex ION. This emphasizes that a strict interpretation

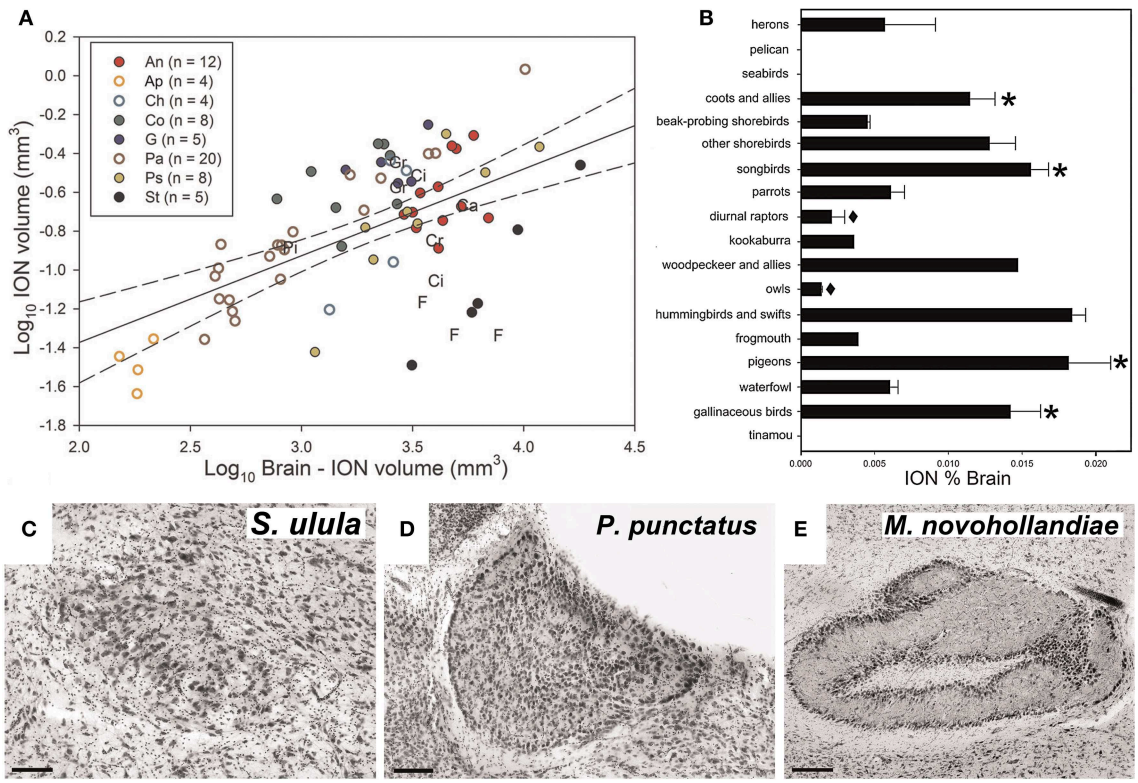


FIGURE 4 | Variation in the volume and complexity of the isthmo optic nucleus (ION). (A) Shows a scatterplot of ION volume plotted as a function of brain minus ION volume (log transformed). *n* indicates to the number of species measured in each order. An, Anseriformes (red full circles); Ap, Apodiformes (empty orange circle); Ca, Caprimulgiforms; Ch, Charadriiforms (empty light blue circle); Ci, Ciconiiformes; Co, Columbiforms (dark green full circles); Cr, Coraciiforms; F, Falconiforms; G, Galliformes (dark blue full circle); Gr, Gruiformes; Pa, Passerifomes (empty brown circles); Pi, Piciforms; Ps, Psittaciformes (full yellow circle); St, Strigiforms (full black circle). **(B)** Shows a bar graph of the relative size of ION expressed as a percentage of total brain volume for the different groups of birds. The error bars indicate standard error. The asterisk (*) indicates the groups in which a lower field myopia has been described (Martin, 1986, 1993; Hodos and Erichsen, 1990; Schaeffel et al., 1994). The black diamond (♦) indicates species where a lack of lower field myopia has been described (Murphy et al., 1995). **(C–E)** Show variation in the complexity of the ION. The ION complexity representative of categories 1, 3, and 5 (most complex) are, respectively, shown in **(C)** (Northern Hawk-Owl, *S. Ulula*), **(D)** (Spotted Pardalote, *P. punctatus*), and **(E)** (Superb Lyrebird, *M. novaehollandiae*). Scale bars, 100 μm in **(C,D)**, 200 μm in **(E)** (Adapted from Gutiérrez-Ibáñez et al., 2012).

of the Principle of Proper Mass (i.e., considering only size) may miss other neuronal features that may also be indicative of a processing capacity.

Based on these data, Gutiérrez-Ibáñez et al. (2012) proposed an alternative theory for ION function. Many of the birds that have a relatively large ION (and relatively complex ION; see below) also have a lower field myopia including: pigeons (Fitzke et al., 1985), songbirds (Martin, 1986), galliforms (Schaeffel et al., 1994), and gruiforms (Hodos and Erichsen, 1990), all which have relatively large IONs (**Figure 4B**). In contrast, owls and diurnal raptors, both of which have small IONs (**Figure 4B**), do not have a lower field myopia (Murphy et al., 1995). (Gutiérrez-Ibáñez et al., 2012) therefore suggested that the ION is involved in switching attention from an emmetropic to a myopic part of the retina (i.e., switching from long range to close range). Gutiérrez-Ibáñez et al. (2012) further linked this to feeding behavior. Birds with large IONs (chickens, pigeons, songbirds, woodpeckers, hummingbirds) feed close to the substrate, which can include the ground, flowers and tree trunks. Many of these birds have a lower field myopia, thus the substrate from which they are feeding would be fall in the myopic part of the retina. In contrast, the birds with smaller IONs feed far from the substrate, or have non-visually guided foraging behaviors (e.g., somatosensory based). Owls and diurnal raptors feed by perch hunting or feeding on the wing (Jaksić and Carothers, 1985) and are therefore some distance from the substrate. The reduced size of the ION in herons and the apparent absence of an ION in seabirds and a pelican (**Figure 4B**) also fits this hypothesis, as seabirds and pelicans usually dive into the water to catch fish, while herons have longs legs that keep their eyes at a considerable distance from the ground when foraging (Martin and Katzir, 1994).

Lack of Hypertrophy in the Tectofugal Pathway

Despite the fact that the tectofugal pathway (TeO, nRt, E; see **Figures 5A–C**) is regarded as the "main" visual pathway and is the primary source of visual input to the avian brain, there is relatively little variation in the relative size of the pathway as a whole or each of the brain regions that comprise this pathway (Iwaniuk et al., 2010). All three structures, TeO, nRt, and E, were somewhat smaller in owls, parrots, and waterfowl (**Figures 5D–F**). Although not included in Iwaniuk et al. (2010), Martin et al. (2007) found that the kiwi (*Apteryx mantelli*) has an even smaller TeO and likely represents a case of tectofugal hypotrophy. This may not reflect a reduction in the tectofugal regions *per se*, but rather an expansion of other regions and pathways. Waterfowl, parrots and owls all have an enlarged telencephalon (Portmann, 1947; Iwaniuk and Hurd, 2005), but have enlarged regions within the telencephalon other than the E. The apparently small tectofugal pathway may thus be a result of an enlarged telencephalon in these groups. At the other end of the spectrum, no species appeared to have a hypertrophied tectofugal pathway.

The isthmal nuclei (Imc, Ipc, Slu), which are closely associated with the tectofugal pathway, scaled with negative allometry relative to brain size, but had isometric (i.e., 1:1) relationships with TeO and nRt (Gutiérrez-Ibáñez et al., 2014). Thus, it seems that all the intimately connected nuclei within the tectofugal system have evolved in concert and that variation in the size of any one is generally accompanied by a similar degree of variation in the others.

The lack of hypertrophy in the tectofugal pathway is in marked contrast to what we observed in LM, Wulst and ION. The lack of such hypertrophy could reflect the heterogeneous organization of the tectofugal pathway, insofar as color, motion, and form are all processed in this pathway (Frost et al., 1988; Wang et al., 1993; Bischof and Watanabe, 1997; Sun and Frost, 1998; Nguyen et al., 2004; Xiao et al., 2006; Xiao and Frost, 2009). The cells within the tectofugal regions are tuned to specific types of visual functions. Within nRt, for example, neurons are tuned to 3D motion ("looming"), 2D motion, luminance and color, with each of these components represented in a separate subregion of the nucleus (Wang et al., 1993). Similarly, form and visual motion are, respectively, represented in rostral and caudal margins of E (Nguyen et al., 2004). These subdivisions cannot be discerned in Nissl stained brain sections, but species could vary in the proportional size of these motion, form, and color-regions, depending on their ecology and behavior. Thus, some birds could require more cells responsive to motion processing vs. color. The relative sizes within nRt and E that respond to motion could then be enlarged at the expense of the color regions without having an effect on the overall size. Neurochemical markers that delineate these subregions or neurophysiological data for a broader range of species would enable us to test this hypothesis in the future.

Brain–behavior Relationships in the Avian Auditory System

Investigations of brain–behavior relationships in birds is not restricted to visual systems. The auditory system has also been examined, especially in owls because of their remarkable sound localization ability, unique morphological specializations, and rather sophisticated, adaptive neural circuitry (Schwartzkopff and Winter, 1960; Payne, 1971; Knudsen et al., 1979; Knudsen, 1999; Takahashi et al., 2003; Whitchurch and Takahashi, 2006; Takahashi, 2010). A rather unique feature that sets some owls apart from others with respect to sound localization is the presence of vertically asymmetrical ears, which has evolved independently several times in owls (Norberg, 1977, 2002). This vertical ear asymmetry is particularly important for localizing sounds in elevation. To localize sound, neurons within the external nucleus of the inferior colliculus (ICx) of the midbrain are tuned to auditory space, but these neurons vary in their receptive fields between asymmetrically and symmetrically eared owls. In owls with vertically asymmetrical ears, these neurons have receptive fields that are restricted in both elevation and azimuth, whereas in owls with vertically symmetrical ears, they are restricted only in azimuth (Knudsen et al., 1977; Knudsen and Konishi, 1978a,b; Wise et al., 1988; Volman and Konishi, 1990). The tuning of both elevation and azimuth enables asymmetrically eared owls to accurately capture prey in complete darkness based solely on acoustic cues whereas symmetrically eared owls cannot (Payne, 1971). In barn owls, the azimuthal and elevational

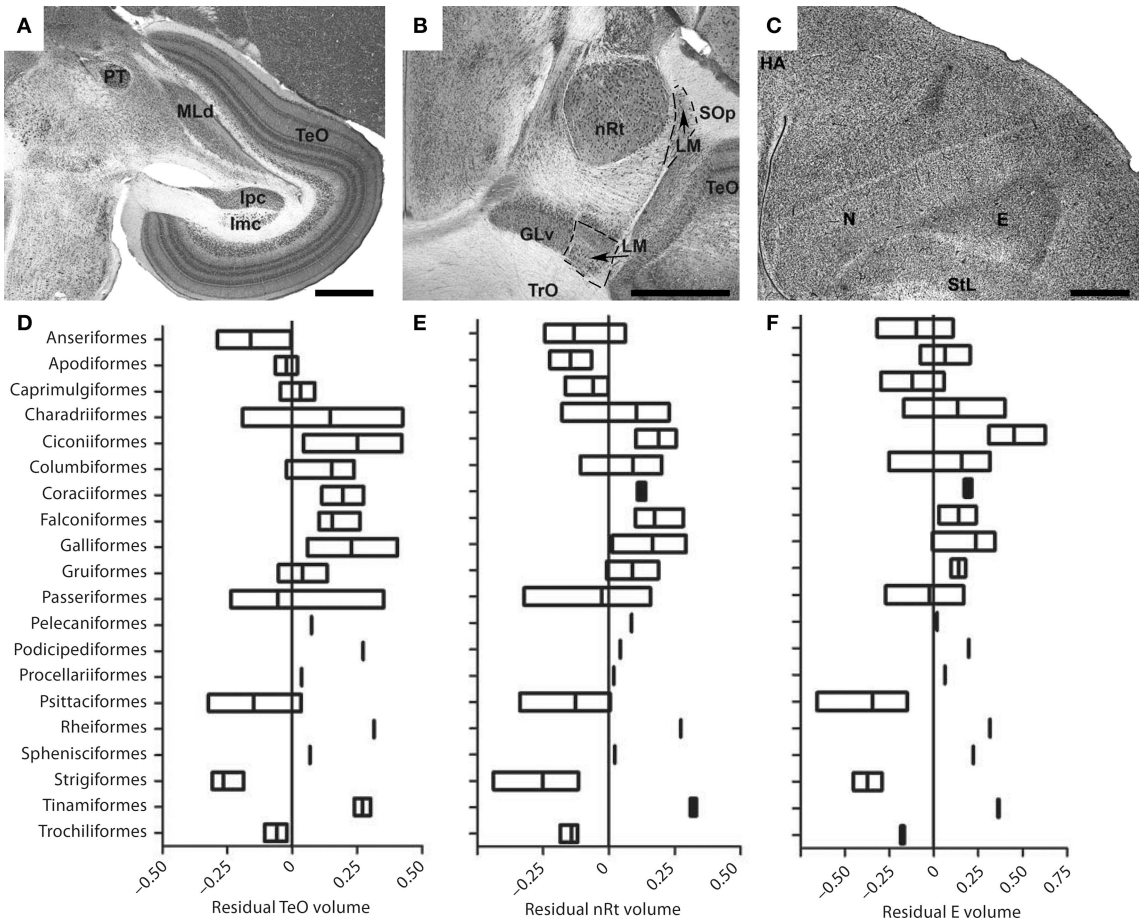


FIGURE 5 | Variation in the size of structures in the tectofugal pathway. (A–C) Show Nissl stained sections highlighting the major nuclei of the tectofugal pathway: the optic tectum (TeO) **(A)**, the nucleus rotundus (nRt) **(B)** and the Entopallium (E) **(C).** The sections in **(A,B)** are from an Eastern Yellow Robin *(E. australis)* whereas that in **(C)** is from a Short-billed Dowitcher *(L. griseus)*. GLv, ventral leaflet of the lateral geniculate nucleus; GP, globus pallidus; HA, hyperpallium apicale; Imc, nucleus isthmi magnocellularis; Ipc, nucleus isthmi parvocellularis; LM, nucleus lentiformis mesencephali; MLd, nucleus mesencephalicus lateralis, pars dorsalis; N, nidopallium; PT, nucleus pretectalis; SOp, stratum opticum; StL, lateral striatum; TrO, optic tract. **(D–F)** Show boxplots showing the variation of the relative size of TeO **(D)**, nRT **(E)**, and Entopallium **(F)**. Scale bars = 1 mm (Adapted from Iwaniuk et al., 2010).

components of a sound locale are computed using interaural time differences (ITDs) and interaural level differences (ILDs), respectively (Knudsen and Konishi, 1979, 1980; Moiseff and Konishi, 1981; Moiseff, 1989). Furthermore, ITDs and ILDs are processed in two separate pathways from the cochlear nuclei to the ICx (Moiseff and Konishi, 1983; Takahashi et al., 1984; Takahashi and Konishi, 1988a,b; Adolphs, 1993; Mazer, 1998). The cochlear nerve projects directly to two nuclei in the brainstem: nucleus angularis (NA) and nucleus magnocellularis (NM) (Carr and Boudreau, 1991). Processing of ILD begins in NA, whereas ITD processing begins with NM (**Figures 6A,B**). NM projects bilaterally to nucleus laminaris (NL) where ITD is first calculated. The ITD and ILD pathways eventually project to different parts of the inferior colliculus (IC) (**Figures 6C,D**) and converge in ICx (Knudsen and Knudsen, 1983; Takahashi et al., 1984; Carr and Konishi, 1990). Given that owls with asymmetrical ears exploit ILDs to compute the elevation of a sound source, Gutiérrez-Ibáñez et al. (2011) hypothesized that the structures in involved in computing ILDs, including NA and the IC, should be larger in owls with vertical asymmetrical ears, whereas there should be no differences in the structures that process only ITD (NM, NL). However, all nuclei in the ITD and ILD pathways were larger in the owls with a vertical ear asymmetry (**Figure 6**). This increase in size of nuclei in both ILD and ITD pathways might be related to a general expansion of hearing range in asymmetrically eared owls. In symmetrically eared owls, audibility deteriorates rapidly above 6 kHz whereas in asymmetrically eared owls the high-frequency cutoff lies between 10 and 13 kHz (Konishi, 1973; Van Dijk, 1973; Dyson et al., 1998). These higher frequency are effectively shadowed by the head such that ILD varies with elevation (Norberg, 1978; Volman and Konishi, 1990). That is, in order to use ILDs to detect localize sound, an asymmetrically eared owl must have high sensitivity to high frequencies. Thus, the

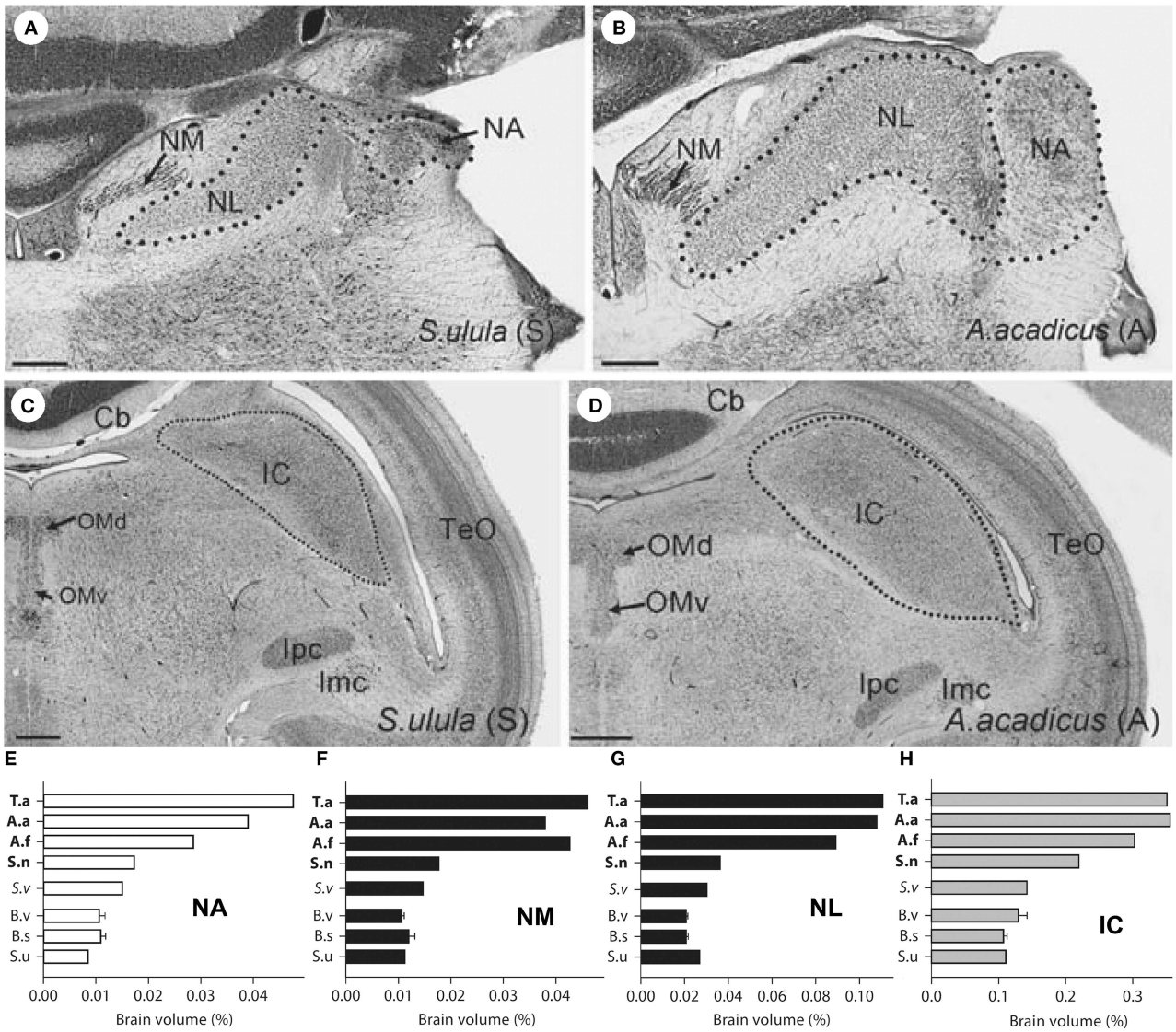


FIGURE 6 | (A–D) Show photomicrographs of coronal section of auditory structures for a symmetrically-eared owl (Northern Hawk Owl, *S. ulula*) **(A,C)** and an asymmetrically-eared owl (Northern Saw-Whet Owl, *A. acadicus*) **(B–D)**. **(A,B)** Emphasize the size differences for the nucleus laminaris, angularis, and magnocellularis (NL, NA, NM) whereas **(C,D)** depict the size difference with respect to the inferior colliculus (IC). TeO, Optic tectum; lpc, parvocellular part of the nucleus isthmi; lmc, magnocellular part of the nucleus isthmi; Cb, cerebellum; OMd/v, dorsal/ventral parts of the oculomotor nucleus. **(E–H)** Are bar graphs showing the sizes of NA **(E)**, NM **(F)**, NL **(G)**, and IC **(H)** expressed as a percentage of total brain volume for eight species of owls. Species abbreviations T.a, Barn owl (*T. alba*); A.a, Northern Saw-Whet owl (*A. acadicus*); A.f, Short-Eared Owl (*A. flammeus*); S.n, Great Gray Owl (*S. nebulosa*); S.v, Barred Owl (*S. varia*); B.v, Great Horned Owl (*B. virginianus*); B.s, Snowy Owl (*B. scandiacus*); S.u, Northern Hawk owl (*S.ulula*). Each species was classified as having a high degree of vertical ear asymmetry (T.a, A.a, A.f, S.n), a moderate degree of ear asymmetry (S.v) or symmetrical ears. (B.v, B.s, S.u) (Adapted from Gutiérrez-Ibáñez et al., 2011).

expansion of the audible range would explain not only the equal enlargement of the ILD pathway, but also the hypertrophy of all auditory nuclei and this has happened several times throughout the evolutionary history of owls. Based on these anatomical differences in owls, one would predict that harriers (*Circus* sp.) also have enlarged auditory nuclei. Harriers are diurnal raptors that have an owl-like facial ruff, hunts in a similar fashion to short-eared owls (*Asio flammeus*) and are capable of resolving azimuth at a similar acuity to owls (Rice, 1982), but neuroanatomical studies of any harrier species are wanting.

Hypertrophy in the Somatosensory System

Finally, we will illustrate an example of Jerison's Principle of Proper Mass as applied to the somatosensory system. Beak size and shape varies immensely among bird species in relation to their foraging behavior and diet. In addition to beak shape,

the number, type and distribution of mechanoreceptors also varies among species (Gottschaldt, 1985) and these features reflect feeding behavior. For example, in beak-probing shorebirds mechanoreceptors are numerous and concentrated in the tip of the beak (Bolze, 1968; Pettigrew and Frost, 1985) whereas in ducks and geese they are more widely distributed across the beak, as well as on the tongue (Berkhoudt, 1979). The beak mechanoreceptors are innervated by the trigeminal nerve (nV; Dubbeldam and Karten, 1978) of which one of the main targets is the principal sensory nucleus of the trigeminal nerve (PrV) (**Figure 7**) (Zeigler and Witkovsky, 1968; Silver and Witkovsky, 1973; Kishida et al., 1985; Dubbeldam, 1998). PrV also receives projections from the facial (nVII), glossopharyngeal (nIX) and hypoglossal (nXII) nerves and thus the PrV gathers information from the beak, palate, tongue, and pharynx (Dubbeldam et al., 1979; Wild, 1981; Bout and Dubbeldam, 1985; Woodson et al., 1995). PrV is hypertrophied in several taxa: beak-probing shorebirds, waterfowl, parrots, and kiwi (Stingelin, 1965; Boire, 1990; Dubbeldam, 1998; Gutiérrez-Ibáñez et al., 2009; Cunningham et al., 2013) (**Figures 7C,D**). Thus, the enlargement of the PrV had evolved at least three times in birds to support three types of feeding behavior, beak-probing (shorebirds and kiwi), filtering (waterfowl), and seed husking (parrots), which all demand processing of mechanoreceptor information from the beak (Zweers et al., 1977, 1994; Berkhoudt, 1979; Gerritsen and Meiboom, 1985; Gottschaldt, 1985; Zweers and Gerritsen, 1996; Piersma et al., 1998; Cunningham et al., 2013).

PrV projects to the somatotopically organized nucleus basorostralis (Bas) in the telencephalon (Witkovsky et al., 1973; Berkhoudt et al., 1981; Dubbeldam et al., 1981; Wild et al., 1985;

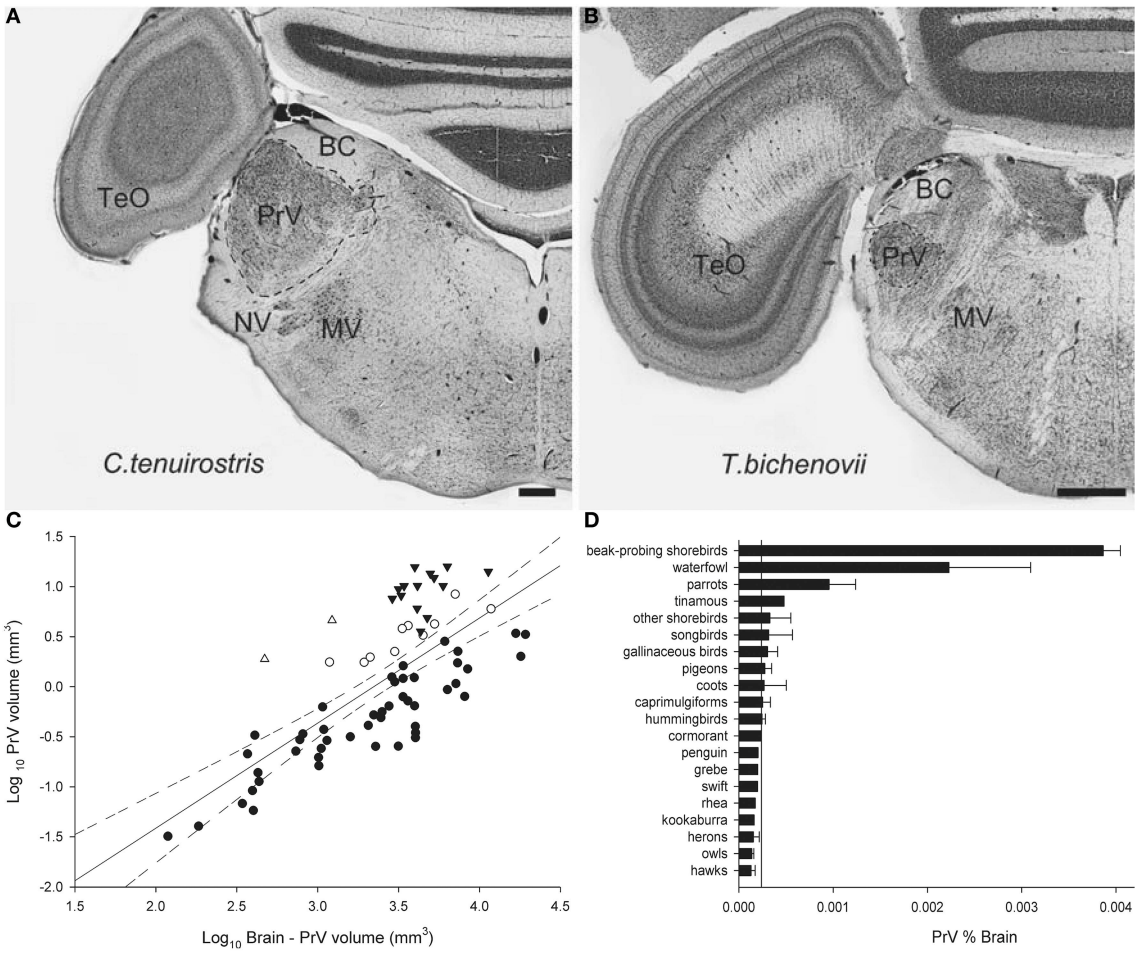


FIGURE 7 | Photomicrographs of coronal sections through the principal sensory nucleus of the trigeminal nerve (PrV) of a somatosensory specialist (A, Long-Billed Corella, *C. tenuirostris*) and a non-specialist (B, Double-Barred Finch, *T. bichenovii*). TeO, optic tectum; BC, brachium conjunctivum; NV, root of the trigeminal nerve; MV, motor nucleus of the trigeminal nerve. **(C)** Shows a scatterplot of PrV volume as a function of brain minus PrV volume for all species examined. Waterfowl are indicated by black triangles, beak-probing shorebirds by white triangles, parrots by white circles, and non-specialists by black circles. **(D)** Is a histogram of the relative size of PrV expressed as a percentage of total brain volume. The solid line indicates the mean for all non-specialists and the error bars indicate standard deviations. Scale bars = 600 μm (Adapted from Gutiérrez-Ibáñez et al., 2009).

Wild and Farabaugh, 1996). The size of Bas varies with that of PrV, but species with an enlarged PrV do not necessarily have an enlarged Bas (Cunningham et al., 2013). Waterfowl, kiwi, and beak-probing shorebirds all have an enlarged PrV and Bas, but parrots only appear to have an enlarged PrV. As with some of the aforementioned comparisons of telencephalic brain regions, this could reflect the expansion of other telencephalic regions in parrots, such as the nidopallium and mesopallium (Iwaniuk and Hurd, 2005), or the fact that Bas is receiving other forms of sensory input. Nevertheless, the Principle of Proper Mass certainly applies to the somatosensory system in birds.

Trade-offs

If you are a somatosensory or auditory specialist, does this come at the expense of sacrificing another sensory system? Brain tissue is among the more energetically expensive as it requires almost an order of magnitude more energy per unit weight than many other tissues (Mink et al., 1981) and is not only expensive to use, but also to maintain (Niven and Laughlin, 2008). The large energy requirements of the brain has been proposed to be a major factor in the evolution of brains in vertebrates (Aiello and Wheeler, 1995; Striedter, 2005; Fonseca-Azevedo and Herculano-Houzel, 2012). The expensive brain hypothesis predicts that relatively large brains can evolve only when either energy input increases (Aiello and Wheeler, 1995; Isler and van Schaik, 2006a) or there is a trade-off that implies reduction of another expensive tissue such as the digestive tract in primates (Aiello and Wheeler, 1995) or the pectoral muscle in birds (Isler and van Schaik, 2006b). Recent selection experiments in fish seem to confirm this hypothesis as selection for larger brains results in the reduction of gut size in only a few generations (Kotrschal et al., 2013). Concordantly, it has also be proposed that trade-offs occur within the brain so that expansion of one area is accompanied by reduction in another. So far, evidence for this trade-off in neural tissue comes mostly from sensory systems. For example, fish species that live permanently in caves have reduced visual system and an expanded lateral line system when compared with surface-dwelling species (Poulson and White, 1969; Niven and Laughlin, 2008; Soares and Niemiller, 2013). In mammals, Baron et al. (1996) found that there is a tradeoff between the relative sizes of auditory and visual structures in the mesencephalon in bats (see also Iwaniuk et al., 2006), and Eisenberg (1981) suggested that a similar trade-off between visual and auditory pathways may occur in tenrecs, which use echolocation and have small eyes. Further, some subterranean mammals, like the star-nosed mole (*Condylura cristata*) or the blind mole rats (*Spalax ehrenbergi*), have reduced thalamo-cortical visual systems and an expanded somatosensory representation, particularly of the trigeminal system (Cooper et al., 1993; Catania and Kaas, 1995).

Although there has been no clear demonstration of trade-offs between sensory systems in birds, there is some evidence that this phenomenon applies to avian sensory systems as well. For example, several groups present a tendency similar to subterranean mammals mentioned above, with a trade-off between the size of visual and trigeminal/somatosensory systems. First, as discussed above, waterfowl, parrots, and kiwi all have an enlarged trigeminal system and a small tectofugal pathway (**Figure 8A**) (Martin et al., 2007; Iwaniuk et al., 2010; Cunningham et al., 2013; Gutiérrez-Ibáñez et al., 2014). An extreme case of this trade-off within waterfowl could be the extinct species *Talpanas lippa* (Iwaniuk et al., 2009), which has a greatly reduced optic foramen and an extremely enlarged maxillo-mandibular (nV) foramen, much larger than any other waterfowl or bird. Second, within the order Charadriformes, there is a clear separation of species into those with a large trigeminal and a small tectofugal pathway and those with a large tectofugal and a small trigeminal pathway (**Figure 8B**). This separation reflects whether they are beak probing species or not. The beak probing sandpipers have a greatly expanded trigeminal system and a small TeO compared to the non-beak probing species (e.g., plovers, terns), which have a much smaller

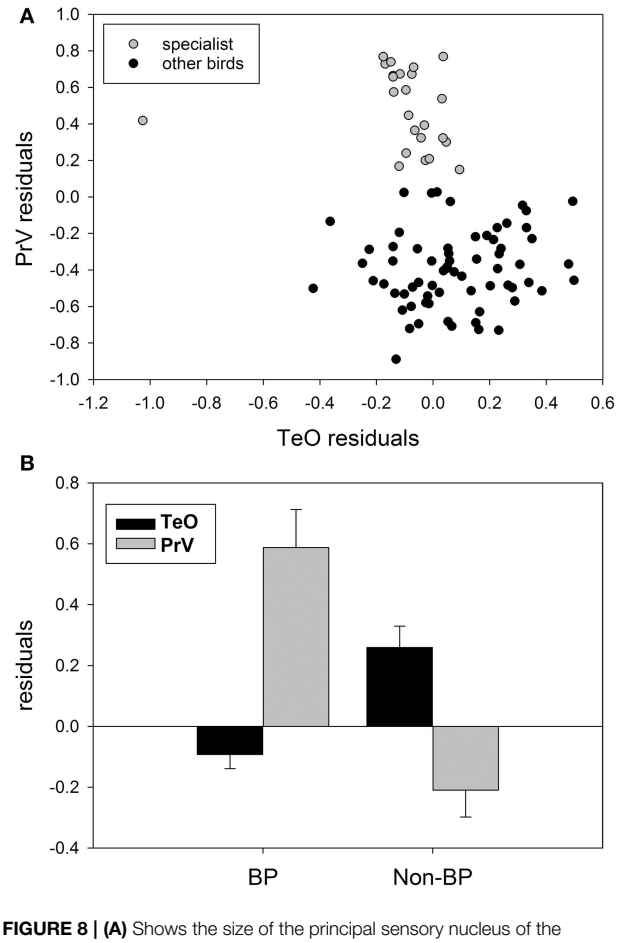


FIGURE 8 | (A) Shows the size of the principal sensory nucleus of the trigeminal nerve (PrV) as a function of the optic tectum (TeO) for somatosensory specialists: parrots waterfowl, beak-probing shorebirds and the kiwi (gray circles) and other birds (black circles). **(B)** Shows a comparison of the relative size of the TeO and PrV for beak-probing (PB) shorebirds and non-beaking-probing (Non-BP) shorebirds. Data from Iwaniuk et al. (2010), Gutiérrez-Ibáñez et al. (2009), and Cunningham et al. (2013).

PrV and a larger TeO. One could even argue that owls and a subset of caprimulgiforms are yet another example of a trade-off, but within a single sensory domain: vision. Owls, frogmouths, and owlet-nightjars have a greatly enlarged thalamofugal system, with a correspondingly smaller tectofugal system (Iwaniuk and Wylie, 2006; Iwaniuk et al., 2010; Gutiérrez-Ibáñez et al., 2013).

Taken together this data suggest that in birds, like in other vertebrates, there are constraints in the evolution of sensory systems such that the enlargement of one sensory pathway is accompanied by the diminution of another sensory pathway. More detailed analyses of a wider range of species is needed to address these contingencies and to determine when and how rapidly these changes occur in evolutionary time. It is worth noting that although sensory trade-offs play a significant role in the evolution of sensory systems, it is certainly not the only factor any more so than phylogeny, allometry or behavior. In the case of the visual system of owls for example, the hypotrophy of the tectofugal pathway is probably related to a reduction in the number of retinal ganglion cells, which, in turn, is likely a result of the nocturnal history of the clade (Gutiérrez-Ibáñez et al., 2013). Thus, sensory trade-offs can only be understood in an integrative context that combines the functional organization of the sensory pathways with anatomy, behavior and phylogeny.

Conclusion

An emerging pattern from the studies reviewed here is that changes in the size and cytoarchitecture of different neural structures occur repeatedly and these changes are largely independent of phylogeny. This is true for almost all the examples reviewed including: PrV (Gutiérrez-Ibáñez et al., 2009; Cunningham et al., 2013), visual wulst (Iwaniuk and Wylie, 2006; Iwaniuk et al., 2008), and the auditory system in asymmetrically eared owls (Gutiérrez-Ibáñez et al., 2011). The majority of these differences reflect "grade shifts" among clades of birds and likely occurred fairly early in the diversification of modern birds. For example, the expansion of PrV in waterfowl likely occurred at or close to the divergence between Galliformes and Anseriformes, which is estimated to be 65 million years ago (Jarvis et al., 2014). With recent advancements in avian genomics of birds (Jarvis et al., 2014; Koepfli et al., 2015), it is now possible to test the relationship between genes and neuroanatomy to obtain insight into the underlying molecular mechanisms responsible for species variation in brain anatomy. Recently, Schneider et al. (2014) showed that *Piezo2* is upregulated in waterfowl compared with galliforms and that this upregulation is related to increases in the number of large diameter fibers in the trigeminal nerve, expansion of PrV and increases tactile sensitivity. If *Piezo2* is an essential component of regulating tactile sensitivity, then it might also be upregulated in parrots, beak-probing shorebirds and kiwi. Similarly, the evolution of a vocal control system is associated with differential expression of two genes involved in axonal guidance (Wang et al., 2015) and even the evolution of novel genes in songbirds (Wirthlin et al., 2014). These two recent examples highlight the strengths and importance of incorporating gene regulation into comparative neuroanatomy to address not only what species differences are present, but also how they have occurred. Now that we are gaining a much more in depth understanding of anatomical variation in the avian brain, we can apply bioinformatics approaches (Mello and Clayton, 2015) to address mechanistic questions, such as "How and why do owls have such an enlarged hyperpallium?." By integrating molecular mechanisms with evolutionary patterns, we will achieve a far deeper understanding of the evolution of the avian brain and behavior.

References

Adolphs, R. (1993). Bilateral inhibition generates neuronal responses tuned to interaural level differences in the auditory brainstem of the barn owl. *J. Neurosci.* 13, 3647–3668.

Aiello, L. C., and Wheeler, P. (1995). The expensive-tissue hypothesis: the brain and the digestive system in human and primate evolution. *Curr. Anthropol.* 36, 199–221. doi: 10.1086/204350

Altshuler, D. L., and Dudley, R. (2002). The ecological and evolutionary interface of hummingbird flight physiology. *J. Exp. Biol.* 205, 2325–2336.

Azevedo, F. A., Carvalho, L. R., Grinberg, L. T., Farfel, J. M., Ferretti, R. E. L., Leite, R. E. P., et al. (2009). Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *J. Comp. Neurol.* 513, 532–541. doi: 10.1002/cne.21974

Baron, G., Stephan, H., and Frahm, H. D. (1996). *Comparative Neurobiology in Chiroptera: in Brain Characteristics in Functional Systems, Ecoethological Adaptation, Adaptive Radiation and Evolution.* Basel: Birkhäuser Verlag.

Baron, J., Pinto, L., Dias, M. O., Lima, B., and Neuenschwander, S. (2007). Directional responses of visual wulst neurones to grating and plaid patterns in the awake owl. *Eur. J. Neurosci.* 26, 1950–1968. doi: 10.1111/j.1460-9568.2007.05783.x

Barton, R. (1998). Visual specialization and brain evolution in primates. *Proc. Biol. Sci.* 265, 1933–1937. doi: 10.1098/rspb.1998.0523

Barton, R. A., Purvis, A., and Harvey, P. H. (1995). Evolutionary radiation of visual and olfactory brain systems in primates, bats and insectivores. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 348, 381–392. doi: 10.1098/rstb.1995.0076

Benowitz, L. I., and Karten, H. J. (1976). Organization of the tectofugal visual pathway in the pigeon: a retrograde transport study. *J. Comp. Neurol.* 167, 503–520. doi: 10.1002/cne.901670407

Berkhoudt, H. (1979). The morphology and distribution of cutaneous mechanoreceptors (herbst and grandry corpuscles) in bill and tongue of the mallard (*Anas Platyrhynchos* L.). *Netherlands J. Zool.* 30, 1–34. doi: 10.1163/002829680X00014

Berkhoudt, H., Dubbeldam, J. L., and Zeilstra, S. (1981). Studies on the somatotopy of the trigeminal system in the mallard, *Anas platyrhynchos* L. IV. Tactile representation in the nucleus basalis. *J. Comp. Neurol.* 196, 407–420. doi: 10.1002/cne.901960305

Bischof, H. J., and Watanabe, S. (1997). On the structure and function of the tectofugal visual pathway in laterally eyed birds. *Eur. J. Morphol.* 35, 246–254. doi: 10.1076/ejom.35.4.246.13080

Boire, D. (1990). *Comparaison Quantitative de l'Encéphale, de ses Grandes Subdivisions et de Relais Visuels, Trijumeaux et Acoustiques chez 28 Especes d'Oiseaux.* Ph.D. thesis, Universite de Montreal, Montreal, Canada.

Bolze, G. (1968). Anordnung und bau der herbstschen korperchen in limicolenschnabeln im zusammenhang mit nahrungsfindung. *Zool. Anz* 181, 313–355.

Bout, R. G., and Dubbeldam, J. L. (1985). An HRP study of the central connections of the facial nerve in the mallard (*Anas platyrhynchos* L.). *Acta Morphol. Neerl. Scand.* 23, 181–193.

Brecha, N. C. (1978). *Some Observations on the Organization of the Avian Optic Tectum: Afferent Nuclei and their Tectal Projections.* Ph.D. Thesis, State University of New York, Stony Brook, New York.

Burns, S., and Wallman, J. (1981). Relation of single unit properties to the oculomotor function of the nucleus of the basal optic root (accessory optic system) in chickens. *Exp. Brain Res.* 42, 171–180. doi: 10.1007/BF00236903

Butler, A. B., and Hodos, W. (2005). *Comparative Vertebrate Neuroanatomy: Evolution and Adaptation*. New York, NY: John Wiley & Sons.

Carr, C. E., and Boudreau, R. E. (1991). Central projections of auditory nerve fibers in the barn owl. *J. Comp. Neurol.* 314, 306–318. doi: 10.1002/cne.903140208

Carr, C. E., and Konishi, M. (1990). A circuit for detection of interaural time differences in the brain stem of the barn owl. *J. Neurosci.* 10, 3227–3246.

Catania, K. C., and Kaas, J. H. (1995). Organization of the somatosensory cortex of the star-nosed mole. *J. Comp. Neurol.* 351, 549–567. doi: 10.1002/cne.903510406

Catsicas, S., Catsicas, M., and Clarke, P. G. (1987). Long-distance intraretinal connections in birds. *Nature* 326, 186–187. doi: 10.1038/326186a0

Clarke, P. G., Gyger, M., and Catsicas, S. (1996). A centrifugally controlled circuit in the avian retina and its possible role in visual attention switching. *Vis. Neurosci.* 13, 1043–1048. doi: 10.1017/S0952523800007690

Cooper, H. M., Herbin, M., and Nevo, E. (1993). Visual system of a naturally microphthalmic mammal: the blind mole rat, *Spalax ehrenbergi*. *J. Comp. Neurol.* 328, 313–350. doi: 10.1002/cne.903280302

Crowder, N. A., Lehmann, H., Parent, M. B., and Wylie, D. R. (2003). The accessory optic system contributes to the spatio-temporal tuning of motion-sensitive pretectal neurons. *J. Neurophysiol.* 90, 1140–1151. doi: 10.1152/jn.00653.2002

Cunningham, S. J., Corfield, J. R., Iwaniuk, A. N., Castro, I., Alley, M. R., Birkhead, T. R., et al. (2013). The anatomy of the bill tip of kiwi and associated somatosensory regions of the brain: comparisons with shorebirds. *PLoS ONE* 8:e80036. doi: 10.1371/journal.pone.0080036

Deaner, R. O., Isler, K., Burkart, J., and van Schaik, C. (2007). Overall brain size, and not encephalization quotient, best predicts cognitive ability across non-human primates. *Brain Behav. Evol.* 70, 115–124. doi: 10.1159/000102973

Denton, C. J. (1981). Topography of the hyperstriatal visual projection area in the young domestic chicken. *Exp. Neurol.* 74, 482–498. doi: 10.1016/0014-4886(81)90186-2

Dooling, R. J., and Fay, R. R. (2000). *Comparative Hearing: Birds and Reptiles*. New York, NY: Springer.

Dubbeldam, J. L. (1998). The sensory trigeminal system in birds: input, organization and effects of peripheral damage. A review. *Arch. Physiol. Biochem.* 106, 338–345. doi: 10.1076/apab.106.5.338.4367

Dubbeldam, J. L., and Karten, H. J. (1978). The trigeminal system in the pigeon (*Columba livia*) I. Projections of the Gasserian ganglion. *J. Comp. Neurol.* 180, 661–678. doi: 10.1002/cne.901800402

Dubbeldam, J. L., Brauch, C. S., and Don, A. (1981). Studies on the somatotopy of the trigeminal system in the mallard, *Anas platyrhynchos* L. III. Afferents and organization of the nucleus basalis. *J. Comp. Neurol.* 196, 391–405. doi: 10.1002/cne.901960304

Dubbeldam, J. L., Brus, E. R., Menken, S. B., and Zeilstra, S. (1979). The central projections of the glossopharyngeal and vagus ganglia in the mallard, *Anas platyrhynchos* L. *J. Comp. Neurol.* 183, 149–168. doi: 10.1002/cne.901830111

Dyson, M. L., Klump, G. M., and Gauger, B. (1998). Absolute hearing thresholds and critical masking ratios in the European barn owl: a comparison with other owls. *J. Comp. Physiol. A* 182, 695–702. doi: 10.1007/s0035900 50214

Eisenberg, J. F. (1981). *The Mammalian Radiations: An Analysis of Trends in Evolution, Adaptation, and Behavior*. Chicago: University of Chicago Press.

Fahrenbach, W. H. (1985). Anatomical circuitry of lateral inhibition in the eye of the horseshoe crab, *Limulus polyphemus*. *Proc. R. Soc. B Biol. Sci.* 225, 219–249. doi: 10.1098/rspb.1985.0060

Felsenstein, J. (1985). Phylogenies and the comparative method. *Am. Nat.* 125, 1–15. doi: 10.1086/284325

Fite, K. V., Brecha, N., Karten, H. J., and Hunt, S. P. (1981). Displaced ganglion cells and the accessory optic system of pigeon. *J. Comp. Neurol.* 195, 279–288. doi: 10.1002/cne.901950208

Fitzke, F. W., Hayes, B. P., Hodos, W., Holden, A. L., and Low, J. C. (1985). Refractive sectors in the visual field of the pigeon eye. *J. Physiol.* 369, 33–44. doi: 10.1113/jphysiol.1985.sp015886

Fonseca-Azevedo, K., and Herculano-Houzel, S. (2012). Metabolic constraint imposes tradeoff between body size and number of brain neurons in human evolution. *Proc. Natl. Acad. Sci. U.S.A.* 109, 18571–18576. doi: 10.1073/pnas.1206390109

Fox, R., Lehmkuhle, S. W, and Bush, R. C. (1977). Stereopsis in the falcon. *Science* 197, 79–81. doi: 10.1126/science.867054

Frost, B. J., Cavanagh, P., and Morgan, B. (1988). Deep tectal cells in pigeons respond to kinematograms. *J. Comp. Physiol. A* 162, 639–647. doi: 10.1007/BF01342639

Frost, B. J., Wylie, D. R., and Wang, Y.-C. (1990). The processing of object and self-motion in the tectofugal and accessory optic pathways of birds. *Vision Res.* 30, 1677–1688. doi: 10.1016/0042-6989(90)90152-B

Frost, B. J., and Nakayama, K. (1983). Single visual neurons code opposing motion independent of direction. *Science* 220, 744–745. doi: 10.1126/science.6836313

Funke, K. (1989). Somatosensory areas in the telencephalon of the pigeon. *Exp. Brain Res.* 76, 620–638. doi: 10.1007/BF00248918

Gamlin, P. D. R. (2006). The pretectum: connections and oculomotor-related roles. *Prog. Brain Res.* 151, 379–405. doi: 10.1016/S0079-6123(05)51012-4

Gamlin, P. D., and Cohen, D. H. (1988). Retinal projections to the pretectum in the pigeon (*Columba livia*). *J. Comp. Neurol.* 269, 1–17. doi: 10.1002/cne.902690102

Garland, T., Dickerman, A. W., Janis, C. M., and Jones, J. A. (1993). Phylogenetic analysis of covariance by computer simulation. *Syst. Biol.* 42, 265–292. doi: 10.1093/sysbio/42.3.265

Gerritsen, A. F. C., and Meiboom, A. (1985). The role of touch in prey density estimation by *Calidris alba*. *Netherlands J. Zool.* 36, 530–561. doi: 10.1163/002829686X00216

Gioanni, H., Rey, J., and Villalobos, J. (1983a). Optokinetic nystagmus in the pigeon (*Columba livia*) II. Role of the pretectal nucleus of the accessory optic system (AOS). *Exp. Brain Res.* 50, 237–247. doi: 10.1007/bf00239188

Gioanni, H., Rey, J., Villalobos, J., and Dalbera, A. (1984). Single unit activity in the nucleus of the basal optic root (nBOR) during optokinetic, vestibular and visuo-vestibular stimulations in the alert pigeon (*Columbia livia*). *Exp. Brain Res.* 57, 49–60. doi: 10.1007/BF00231131

Gioanni, H., Villalobos, J., Rey, J., and Dalbera, A. (1983b). Optokinetic nystagmus in the pigeon (*Columba livia*) III. Role of the nucleus ectomamillaris (nEM): interactions in the accessory optic system (AOS). *Exp. Brain Res.* 50, 248–258. doi: 10.1007/bf00239189

Giolli, R. A., Blanks, R. H. I., and Lui, F. (2006). The accessory optic system: basic organization with an update on connectivity, neurochemistry, and function. *Prog. Brain Res.* 151, 407–440. doi: 10.1016/S0079-6123(05)51013-6

Goller, B., and Altshuler, D. L. (2014). Hummingbirds control hovering flight by stabilizing visual motion. *Proc. Natl. Acad. Sci. U.S.A.* 111, 18375–18380. doi: 10.1073/pnas.1415975111

Gottschaldt, K. (1985). "Structure and function of avian somatosensory receptors," in *Form and Function in Birds,* Vol. 3, eds A. King and J. McLelland (London: Academic Press), 375–461.

Grasse, K., and Cynader, M. (1990). "The accessory optic system in frontal-eyed animals," in *Vision and Visual Dysfunction, Vol. 4. The Neuronal Basis of Visual Function*, ed A. Leventhal (New York, NY: MacMillan), 111–139.

Güntürkün, O., and Remy, M. (1990). The topographical projection of the nucleus isthmi pars parvocellularis (Ipc) onto the tectum opticum in the pigeon. *Neurosci. Lett.* 111, 18–22. doi: 10.1016/0304-3940(90)90337-9

Gutiérrez-Ibáñez, C., Iwaniuk, A. N., and Wylie, D. R. (2009). The independent evolution of the enlargement of the principal sensory nucleus of the trigeminal nerve in three different groups of birds. *Brain. Behav. Evol.* 74, 280–294. doi: 10.1159/000270904

Gutiérrez-Ibáñez, C., Iwaniuk, A. N., and Wylie, D. R. (2011). Relative size of auditory pathways in symmetrically and asymmetrically eared owls. *Brain. Behav. Evol.* 78, 286–301. doi: 10.1159/000330359

Gutiérrez-Ibáñez, C., Iwaniuk, A. N., Lisney, T. J., and Wylie, D. R. (2013). Comparative study of visual pathways in owls (aves: strigiformes). *Brain. Behav. Evol.* 81, 27–39. doi: 10.1159/000343810

Gutiérrez-Ibáñez, C., Iwaniuk, A. N., Lisney, T. J., Faunes, M., Marín, G. J., and Wylie, D. R. (2012). Functional implications of species differences in the

size and morphology of the isthmo optic nucleus (ION) in birds. *PLoS ONE* 7:e37816. doi: 10.1371/journal.pone.0037816

Gutiérrez-Ibáñez, C., Iwaniuk, A. N., Moore, B. A., Fernández-Juricic, E., Corfield, J. R., Krilow, J. M., et al. (2014). Mosaic and concerted evolution in the visual system of birds. *PLoS ONE* 9:e90102. doi: 10.1371/journal.pone.0090102

Hackett, S. J., Kimball, R. T., Reddy, S., Bowie, R. C. K., Braun, E. L., Braun, M. J., et al. (2008). A phylogenomic study of birds reveals their evolutionary history. *Science* 320, 1763–1768. doi: 10.1126/science.1157704

Hahmann, U., and Güntürkün, O. (1992). Visual-discrimination deficits after lesions of the centrifugal visual system in pigeons (*Columba livia*). *Vis. Neurosci.* 9, 225. doi: 10.1017/S0952523800010634

Hartline, H. K., and Ratliff, F. (1972). "Inhibitory interaction in the retina of Limulus," in *Physiology of Photoreceptor Organs*, ed M. G. Fuortes (Springer), 381–447.

Harvey, P. H., and Pagel, M. (1991). *Comparative Method in Evolutionary Biology*. Oxford: Oxford University Press.

Healy, S. D., and Rowe, C. (2007). A critique of comparative studies of brain size. *Proc. R. Soc. B Biol. Sci.* 274, 453–464. doi: 10.1098/rspb.2006.3748

Hellmann, B., and Güntürkün, O. (1999). Visual-field-specific heterogeneity within the tecto-rotundal projection of the pigeon. *Eur. J. Neurosci.* 11, 2635–2650. doi: 10.1046/j.1460-9568.1999.00681.x

Hellmann, B., and Güntürkün, O. (2001). Structural organization of parallel information processing within the tectofugal visual system of the pigeon. *J. Comp. Neurol.* 429, 94–112. doi: 10.1002/1096-9861(20000101)429:1<94::AID-CNE8>3.0.CO;2-5

Hellmann, B., Güntürkün, O., and Manns, M. (2004). Tectal mosaic: organization of the descending tectal projections in comparison to the ascending tectofugal pathway in the pigeon. *J. Comp. Neurol.* 472, 395–410. doi: 10.1002/cne.20056

Herculano-Houzel, S. (2009). The human brain in numbers: a linearly scaled-up primate brain. *Front. Hum. Neurosci.* 3:31. doi: 10.3389/neuro.09.031.2009

Herculano-Houzel, S., Collins, C. E., Wong, P., and Kaas, J. H. (2007). Cellular scaling rules for primate brains. *Proc. Natl. Acad. Sci. U.S.A.* 104, 3562–3567. doi: 10.1073/pnas.0611396104

Hill, K. M., and DeVoogd, T. J. (1991). Altered daylength affects dendritic structure in a song-related brain region in red-winged blackbirds. *Behav. Neural Biol.* 56, 240–250. doi: 10.1016/0163-1047(91)90379-5

Hodos, W., and Erichsen, J. T. (1990). Lower-field myopia in birds: an adaptation that keeps the ground in focus. *Vision Res.* 30, 653–657. doi: 10.1016/0042-6989(90)90091-X

Holden, A. L. (1968). Antidromic activation of the isthmo-optic nucleus. *J. Physiol.* 197, 183–198. doi: 10.1113/jphysiol.1968.sp008554

Hunt, S. P., and Künzle, H. (1976). Observations on the projections and intrinsic organization of the pigeon optic tectum: an autoradiographic study based on anterograde and retrograde, axonal and dendritic flow. *J. Comp. Neurol.* 170, 153–172. doi: 10.1002/cne.901700203

Hunt, S. P., and Webster, K. E. (1975). The projection of the retina upon the optic tectum of the pigeon. *J. Comp. Neurol.* 162, 433–445. doi: 10.1002/cne.901620403

Husband, S., and Shimizu, T. (2001). "Evolution of the avian visual system," in *Avian Visual Cognition,* ed R. G. Cook. Available online at: www.pigeon.psy.tufts.edu/avc

Isler, K., and van Schaik, C. (2006b). Costs of encephalization: the energy trade-off hypothesis tested on birds. *J. Hum. Evol.* 51, 228–243. doi: 10.1016/j.jhevol.2006.03.006

Isler, K., and van Schaik, C. P. (2006a). Metabolic costs of brain size evolution. *Biol. Lett.* 2, 557–560. doi: 10.1098/rsbl.2006.0538

Ito, M. (1984). *The Cerebellum and Neural Control*. New York, NY: Raven Pr.

Iwaniuk, A. (2004). Brood parasitism and brain size in cuckoos: a cautionary tale on the use of modern comparative methods. *Int. J. Comp. Psychol.* 17, 17–33.

Iwaniuk, A. N., and Hurd, P. L. (2005). The evolution of cerebrotypes in birds. *Brain Behav. Evol.* 65, 215–230. doi: 10.1159/000084313

Iwaniuk, A. N., and Wylie, D. R. W. (2006). The evolution of stereopsis and the Wulst in caprimulgiform birds: a comparative analysis. *J. Comp. Physiol. A* 192, 1313–1326. doi: 10.1007/s00359-006-0161-2

Iwaniuk, A. N., and Wylie, D. R. W. (2007). Neural specialization for hovering in hummingbirds: hypertrophy of the pretectal nucleus lentiformis mesencephali. *J. Comp. Neurol.* 500, 211–221. doi: 10.1002/cne.21098

Iwaniuk, A. N., Clayton, D. H., and Wylie, D. R. W. (2006). Echolocation, vocal learning, auditory localization and the relative size of the avian auditory midbrain nucleus (MLd). *Behav. Brain Res.* 167, 305–317. doi: 10.1016/j.bbr.2005.09.015

Iwaniuk, A. N., Dean, K. M., and Nelson, J. E. (2004). A mosaic pattern characterizes the evolution of the avian brain. *Proc. Biol. Sci.* 271(Suppl.), S148–S151. doi: 10.1098/rsbl.2003.0127

Iwaniuk, A. N., Gutierrez-Ibanez, C., Pakan, J. M. P., and Wylie, D. R. (2010). Allometric scaling of the tectofugal pathway in birds. *Brain Behav. Evol.* 75, 122–137. doi: 10.1159/000311729

Iwaniuk, A. N., Heesy, C. P., Hall, M. I., and Wylie, D. R. W. (2008). Relative Wulst volume is correlated with orbit orientation and binocular visual field in birds. *J. Comp. Physiol. A* 194, 267–282. doi: 10.1007/s00359-007-0304-0

Iwaniuk, A. N., Nelson, J. E., and Pellis, S. M. (2001). Do big-brained animals play more? Comparative analyses of play and relative brain size in mammals. *J. Comp. Psychol.* 115, 29–41. doi: 10.1037/0735-7036.115.1.29

Iwaniuk, A. N., Olson, S. L., and James, H. F. (2009). Extraordinary cranial specialization in a new genus of extinct duck (Aves: Anseriformes) from Kauai, Hawaiian Islands. *Zootaxa* 2296, 47–67.

Jaksić, F. M., and Carothers, J. H. (1985). Ecological, morphological, and bioenergetic correlates of hunting mode in hawks and owls. *Ornis Scand.* 16, 165–172. doi: 10.2307/3676627

Jarvis, E. D., Mirarab, S., Aberer, A. J., Li, B., Houde, P., Li, C., et al. (2014). Whole-genome analyses resolve early branches in the tree of life of modern birds. *Science* 346, 1320–1331. doi: 10.1126/science.1253451

Jerison, H. (1973). *Evolution of the Brain and Intelligence*. New York: Academic Press.

Karten, H. J., and Shimizu, T. (1989). The origins of neocortex: connections and lamination as distinct events in evolution. *J. Cogn. Neurosci.* 1, 291–301. doi: 10.1162/jocn.1989.1.4.291

Karten, H. J., Hodos, W., Nauta, W. J., and Revzin, A. M. (1973). Neural connections of the "visual wulst" of the avian telencephalon. Experimental studies in the piegon (*Columba livia*) and owl (*Speotyto cunicularia*). *J. Comp. Neurol.* 150, 253–278. doi: 10.1002/cne.901500303

Karten, J. H., Fite, K. V., and Brecha, N. (1977). Specific projection of displaced retinal ganglion cells upon the accessory optic system in the pigeon (*Columbia livia*). *Proc. Natl. Acad. Sci. U.S.A.* 74, 1753–1756. doi: 10.1073/pnas.74.4.1753

Katzir, G., and Martin, G. R. (1999). Visual fields in short-toed eagles, *Circaetus gallicus* (Accipitridae), and the function of binocularity in birds. *Brain Behav. Evol.* 53, 55–66. doi: 10.1159/000006582

Kishida, R., Dubbeldam, J. L., and Goris, R. C. (1985). Primary sensory ganglion cells projecting to the principal trigeminal nucleus in the mallard, *Anas platyrhynchos*. *J. Comp. Neurol.* 240, 171–179. doi: 10.1002/cne.902400207

Knipling, R. R. (1978). No deficit in near-field visual acuity of pigeons after transection of the isthmo-optic tract. *Physiol. Behav.* 21, 813–816. doi: 10.1016/0031-9384(78)90022-7

Knudsen, E. I. (1999). Mechanisms of experience-dependent plasticity in the auditory localization pathway of the barn owl. *J. Comp. Physiol. A* 185, 305–321. doi: 10.1007/s003590050391

Knudsen, E. I., and Knudsen, P. F. (1983). Space-mapped auditory projections from the inferior colliculus to the optic tectum in the barn owl (*Tyto alba*). *J. Comp. Neurol.* 218, 187–196. doi: 10.1002/cne.902180206

Knudsen, E. I., and Konishi, M. (1978a). Space and frequency are represented separately in auditory midbrain of the owl. *J. Neurophysiol.* 41, 870–884.

Knudsen, E. I., and Konishi, M. (1979). Mechanisms of sound localization in the barn owl (*Tyto alba*). *J. Comp. Physiol. A* 133, 13–21. doi: 10.1007/BF00663106

Knudsen, E. I., and Konishi, M. (1980). Monaural occlusion shifts receptive-field locations of auditory midbrain units in the owl. *J. Neurophysiol.* 44, 687–695.

Knudsen, E. I., and Konishi, M. (1978b). A neural map of auditory space in the owl. *Science* 200, 795–797.

KPnudsen, E., Blasdel, G., and Konishi, M. (1979). Sound localization by the barn owl (*Tyto alba*) measured with the search coil technique. *J. Comp. Physiol.* 133, 1–11. doi: 10.1007/bf00663105

Knudsen, E. I., Konishi, M., and Pettigrew, J. (1977). Receptive fields of auditory neurons in the owl. *Science* 198, 1278–1280. doi: 10.1126/science.929202

Koepfli, K.-P., Paten, B., and O'Brien, S. J. (2015). The genome 10K project: a way forward. *Annu. Rev. Anim. Biosci.* 3, 57–111. doi: 10.1146/annurev-animal-090414-014900

Konishi, M. (1973). How the owl tracks its prey. *Am. Sci.* 61, 414–424.

Kotrschal, A., Rogell, B., Bundsen, A., Svensson, B., Zajitschek, S., Brännström, I., et al. (2013). Artificial selection on relative brain size in the guppy reveals costs and benefits of evolving a larger brain. *Curr. Biol.* 23, 168–171. doi: 10.1016/j.cub.2012.11.058

Laverghetta, A. V., and Shimizu, T. (2003). Organization of the ectostriatum based on afferent connections in the zebra finch (*Taeniopygia guttata*). *Brain Res.* 963, 101–112. doi: 10.1016/S0006-8993(02)03949-5

Lefebvre, L., Reader, S. M., and Sol, D. (2004). Brains, innovations and evolution in birds and primates. *Brain Behav. Evol.* 63, 233–246. doi: 10.1159/000076784

Lindenfors, P., Nunn, C. L., and Barton, R. A. (2007). Primate brain architecture and selection in relation to sex. *BMC Biol.* 5:20. doi: 10.1186/1741-7007-5-20

Luksch, H., Cox, K., and Karten, H. J. (1998). Bottlebrush dendritic endings and large dendritic fields: motion-detecting neurons in the tectofugal pathway. *J. Comp. Neurol.* 396, 399–414.

Manger, P. R., Elston, G. N., and Pettigrew, J. D. (2002). Multiple maps and activity-dependent representational plasticity in the anterior Wulst of the adult barn owl (*Tyto alba*). *Eur. J. Neurosci.* 16, 743–750. doi: 10.1046/j.1460-9568.2002.02119.x

Marin, G. J., Duran, E., Morales, C., Gonzalez-Cabrera, C., Sentis, E., Mpodozis, J., et al. (2012). Attentional capture? Synchronized feedback signals from the isthmi boost retinal signals to higher visual areas. *J. Neurosci.* 32, 1110–1122. doi: 10.1523/JNEUROSCI.4151-11.2012

Marin, G., Letelier, J. C., and Wallman, J. (1990). Saccade-related responses of centrifugal neurons projecting to the chicken retina. *Exp. Brain Res.* 82, 263–270. doi: 10.1007/BF00231246

Marín, G., Letelier, J. C., Henny, P., Sentis, E., Farfán, G., Fredes, F., et al. (2003). Spatial organization of the pigeon tectorotundal pathway: an interdigitating topographic arrangement. *J. Comp. Neurol.* 458, 361–380. doi: 10.1002/cne.10591

Marín, G., Salas, C., Sentis, E., Rojas, X., Letelier, J. C., and Mpodozis, J. (2007). A cholinergic gating mechanism controlled by competitive interactions in the optic tectum of the pigeon. *J. Neurosci.* 27, 8112–8121. doi: 10.1523/JNEUROSCI.1420-07.2007

Martin, G. R. (1984). The visual fields of the tawny owl, *Strix aluco* L. *Vision Res.* 24, 1739–1751. doi: 10.1016/0042-6989(84)90005-1

Martin, G. R. (1986). The eye of a passeriform bird, the European starling (*Sturnus vulgaris*): eye movement amplitude, visual fields and schematic optics. *J. Comp. Physiol. A* 159, 545–557. doi: 10.1007/BF00604174

Martin, G. R. (1993). "Producing the image," in *Vision Brain, and Behaviour in Birds,* eds H. P. Zeigler and H. J. Bischof (Cambridge, MA: MIT Press), 5–24.

Martin, G. R. (2009). What is binocular vision for? A birds' eye view. *J. Vis.* 9, 14.1–19. doi: 10.1167/9.11.14

Martin, G. R., and Coetzee, H. C. (2004). Visual fields in hornbills: precision-grasping and sunshades. *IBIS* 146, 18–26. doi: 10.1111/j.1474-919X.2004.00211.x

Martin, G. R., and Katzir, G. (1994). visual fields and eye movements in herons (Ardeidae). *Brain Behav. Evol.* 44, 74–85. doi: 10.1159/000113571

Martin, G. R., Rojas, L. M., Figueroa, Y. M. R., and McNeil, R. (2004a). Binocular vision and nocturnal activity in Oilbirds (*Steatornis caripensis*) and Pauraques (*Nyctidromus albicollis*): Caprimulgiformes. *Ornitol. Neotrop.* 15, 233–242.

Martin, G. R., Wilson, K.-J., Martin Wild, J., Parsons, S., Fabiana Kubke, M., and Corfield, J. (2007). Kiwi forego vision in the guidance of their nocturnal activities. *PLoS ONE* 2:e198. doi: 10.1371/journal.pone.0000198

Martin, G., Rojas, L. M., Ramírez, Y., and McNeil, R. (2004b). The eyes of oilbirds (*Steatornis caripensis*): pushing at the limits of sensitivity. *Naturwissenschaften* 91, 26–29. doi: 10.1007/s00114-003-0495-3

Mazer, J. A. (1998). How the owl resolves auditory coding ambiguity. *Proc. Natl. Acad. Sci.* 95, 10932–10937. doi: 10.1073/pnas.95.18.10932

Medina, L., and Reiner, A. (2000). Do birds possess homologues of mammalian primary visual, somatosensory and motor cortices? *Trends Neurosci.* 23, 1–12. doi: 10.1016/S0166-2236(99)01486-1

Mello, C. V., and Clayton, D. F. (2015). The opportunities and challenges of large-scale molecular approaches to songbird neurobiology. *Neurosci. Biobehav. Rev.* 50, 70–76. doi: 10.1016/j.neubiorev.2014.09.017

Melvill-Jones, G. (2000). "The cerebellum plays a key role in adapting vestibulo-ocular control," in *Principles of Neural Science, 4th Edn.,* eds E. R. Kandel, J. H. Schwartz, and T. M. Jessell (New York, NY: McGraw-Hill), 825–828.

Miceli, D., and Repérant, J. (1985). Telencephalic afferent projections from the diencephalon and brainstem in the pigeon. A retrograde multiple-label fluorescent study. *Exp. Biol.* 44, 71–99.

Michael, N., Löwel, S., and Bischof, H.-J. (2015). Features of the retinotopic representation in the visual wulst of a laterally eyed bird, the zebra finch (*Taeniopygia guttata*). *PLoS ONE* 10:e0124917. doi: 10.1371/journal.pone.0124917

Miles, F. A., and Wallman, J. (1993). *Visual Motion and Its Role in the Stabilization of Gaze*. Amsterdam: Elsevier Science Ltd.

Mink, J. W., Blumenschine, R. J., and Adams, D. B. (1981). Ratio of central nervous system to body metabolism in vertebrates: its constancy and functional basis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 241, R203–R212.

Moiseff, A. (1989). Bi-coordinate sound localization by the barn owl. *J. Comp. Physiol. A* 164, 637–644. doi: 10.1007/BF00614506

Moiseff, A., and Konishi, M. (1981). Neuronal and behavioral sensitivity to binaural time differences in the owl. *J. Neurosci.* 1, 40–48.

Moiseff, A., and Konishi, M. (1983). Binaural characteristics of units in the owl's brainstem auditory pathway: precursors of restricted spatial receptive fields. *J. Neurosci.* 3, 2553–2562.

Moore, J. M., Székely, T., Büki, J., and Devoogd, T. J. (2011). Motor pathway convergence predicts syllable repertoire size in oscine birds. *Proc. Natl. Acad. Sci. U.S.A.* 108, 16440–16445. doi: 10.1073/pnas.1102077108

Morgan, B., and Frost, B. J. (1981). Visual response characteristics of neurons in nucleus of basal optic root of pigeons. *Exp. Brain Res.* 42, 181–188. doi: 10.1007/BF00236904

Mpodozis, J., Letelier, J., and Concha, M. L. (1995). Retino-tectal and retino-thalamic Visual phatways of the pigeon (*Columba livia*). *Int. J. Neurosci.* 81, 123–136. doi: 10.3109/00207459509015304

Murphy, C. J., Howland, M., and Howland, H. C. (1995). Raptors lack lower-field myopia. *Vision Res.* 35, 1153–1155. doi: 10.1016/0042-6989(94)00240-M

Nguyen, A. P., Spetch, M. L., Crowder, N. A., Winship, I. R., Hurd, P. L., and Wylie, D. R. W. (2004). A dissociation of motion and spatial-pattern vision in the avian telencephalon: implications for the evolution of "visual streams." *J. Neurosci.* 24, 4962–4970. doi: 10.1523/JNEUROSCI.0146-04.2004

Nickla, D. L., Gottlieb, M. D., Marin, G., Rojas, X., Britto, L. R. G., and Wallman, J. (1994). The retinal targets of centrifugal neurons and the retinal neurons projecting to the accessory optic system. *Vis. Neurosci.* 11, 401–409. doi: 10.1017/S0952523800001747

Nieder, A., and Wagner, H. (2000). Horizontal-disparity tuning of neurons in the visual forebrain of the behaving barn owl. *J. Neurophysiol.* 83, 2967–2979.

Nieder, A., and Wagner, H. (2001). Encoding of both vertical and horizontal disparity in random-dot stereograms by Wulst neurons of awake barn owls. *Vis. Neurosci.* 18, 541–547. doi: 10.1017/S0952523801 18404X

Niven, J. E., and Laughlin, S. B. (2008). Energy limitation as a selective pressure on the evolution of sensory systems. *J. Exp. Biol.* 211, 1792–1804. doi: 10.1242/jeb.017574

Nixdorf, B. E., and Bischof, H.-J. (1982). Afferent connections of the ectostriatum and visual wulst in the zebra finch (*Taeniopygia guttata* castanotis Gould)—an HRP study. *Brain Res.* 248, 9–17. doi: 10.1016/0006-8993(82) 91142-8

Norberg, R. (2002). "Independent evolution of outer ear asymmetry among five owl lineages; morphology, function and selection," in *Ecology and Conservation of Owls,* ed I. Newton (Collingwood, VIC: CSIRO), 329–342.

Norberg, R. A. (1977). Occurrence and independent evolution of bilateral ear asymmetry in owls and implications on owl taxonomy. *Philos. Trans. R. Soc. B Biol. Sci.* 280, 375–408. doi: 10.1098/rstb.1977.0116

Norberg, R. A. (1978). Skull asymmetry, ear structure and function, and auditory localization in tengmalm's owl, *Aegolius funereus* (Linne). *Philos. Trans. R. Soc. B Biol. Sci.* 282, 325–410. doi: 10.1098/rstb.1978.0014

Pagel, M. (1999). Inferring the historical patterns of biological evolution. *Nature* 401, 877–884. doi: 10.1038/44766

Payne, R. S. (1971). Acoustic location of prey by barn owls (*Tyto Alba*). *J. Exp. Biol.* 54, 535–573.

Pellis, S. M., and Iwaniuk, A. N. (2002). Brain system size and adult–adult play in primates: a comparative analysis of the roles of the non-visual neocortex and the amygdala. *Behav. Brain Res.* 134, 31–39. doi: 10.1016/S0166-4328(01)00455-7

Pérez-Barbería, F. J., Shultz, S., and Dunbar, R. I. M. (2007). Evidence for coevolution of sociality and relative brain size in three orders of mammals. *Evolution* 61, 2811–2821. doi: 10.1111/j.1558-5646.2007.00229.x

Pettigrew, J. D. (1978). "Comparison of the retinotopic organization of the visual wulst in nocturnal and diurnal raptors, with a note on the evolution of frontal vision," in *Frontiers in Visual Science*, eds D. S. J. Cool and D. E. L. Smith (Berlin; Heidelberg: Springer), 328–335.

Pettigrew, J. D. (1979). Binocular visual processing in the owl's telencephalon. *Proc. R. Soc. B Biol. Sci.* 204, 435–454. doi: 10.1098/rspb.1979.0038

Pettigrew, J. D. (1986). "Evolution of binocular vision," in *Visual Neuroscience*, eds J. Pettigrew, K. Sanderson, and W. Levick (Cambridge: Cambridge University Press), 208–222.

Pettigrew, J. D., and Frost, B. J. (1985). A Tactile Fovea in the *Scolopacidae? Brain Behav. Evol.* 26, 185–195. doi: 10.1159/000118775

Pettigrew, J. D., and Konishi, M. (1984). Some observations on the visual system of the oilbird, *Steatornis caripensis*. *Nat. Geogr. Soc. Res. Rep.* 16, 439–450.

Pettigrew, J. D., and Konishi, M. (1976). Neurons selective for orientation and binocular disparity in the visual Wulst of the barn owl (*Tyto alba*). *Science* 193, 675–678. doi: 10.1126/science.948741

Piersma, T., van Aelst, R., Kurk, K., Berkhoudt, H., and Maas, L. R. M. (1998). A new pressure sensory mechanism for prey detection in birds: the use of principles of seabed dynamics? *Proc. R. Soc. B Biol. Sci.* 265, 1377–1383. doi: 10.1098/rspb.1998.0445

Porciatti, V., Fontanesi, G., Raffaelli, A., and Bagnoli, P. (1990). Binocularity in the little owl, *Athene noctua*. *Brain Behav. Evol.* 35, 40–48. doi: 10.1159/000115855

Portmann, A. (1947). Études sur la cérébralisation chez les oiseaux: II Les indices intra céré- braux. *Alauda* 15, 1–15.

Poulson, T. L., and White, W. B. (1969). The cave environment. *Science* 165, 971–981. doi: 10.1126/science.165.3897.971

Reiner, A., Brecha, N., and Karten, H. J. (1979). A specific projection of retinal displaced ganglion cells to the nucleus of the basal optic root in the chicken. *Neuroscience* 4, 1679–1688. doi: 10.1016/0306-4522(79)90027-7

Reiner, A., Yamamoto, K., and Karten, H. J. (2005). Organization and evolution of the avian forebrain. *Anat. Rec. A Discov. Mol. Cell. Evol. Biol.* 287, 1080–1102. doi: 10.1002/ar.a.20253

Remy, M., and Güntürkün, O. (1991). Retinal afferents to the tectum opticum and the nucleus opticus principalis thalami in the pigeon. *J. Comp. Neurol.* 305, 57–70. doi: 10.1002/cne.903050107

Repérant, J., Miceli, D., Vesselkin, N. P., and Molotchnikoff, S. (1989). The centrifugal visual system of vertebrates: a century-old search reviewed. *Int. Rev. Cytol.* 118, 115–171. doi: 10.1016/S0074-7696(08)60874-8

Repérant, J., Ward, R., Miceli, D., Rio, J. P., Médina, M., Kenigfest, N. B., et al. (2006). The centrifugal visual system of vertebrates: a comparative analysis of its functional anatomical organization. *Brain Res. Rev.* 52, 1–57. doi: 10.1016/j.brainresrev.2005.11.008

Revell, L. J. (2010). Phylogenetic signal and linear regression on species data. *Methods Eco. Evol.* 1, 319–329. doi: 10.1111/j.2041-210x.2010.00044.x

Rice, W. R. (1982). Acoustical location of prey by the marsh hawk: adaptation to concealed prey. *Auk* 99, 403–413.

Rogers, L. J., and Miles, F. A. (1972). Centrifugal control of the avian retina. V. Effects of lesions of the isthmo-optic nucleus on visual behaviour. *Brain Res.* 48, 147–156. doi: 10.1016/0006-8993(72)90175-8

Schaeffel, F., Hagel, G., Eikermann, J., and Collett, T. (1994). Lower-field myopia and astigmatism in amphibians and chickens. *J. Opt. Soc. Am. A* 11: 487. doi: 10.1364/josaa.11.000487

Schneider, E. R., Mastrotto, M., Laursen, W. J., Schulz, V. P., Goodman, J. B., Funk, O. H., et al. (2014). Neuronal mechanism for acute mechanosensitivity in tactile-foraging waterfowl. *Proc. Natl. Acad. Sci. U.S.A.* 111, 14941–14946. doi: 10.1073/pnas.1413656111

Schuchmann. (1999). "Family Trochilidae (Hummingbirds)," in *Handbook of the birds of the world*, *Vol. 5: Barn-owls to Hummingbirds,* eds J. Del Hoyo, A. Elliot, and J. Sargata (Lynx: Barcelona), 468–680.

Schwartzkopff, J., and Winter, P. (1960). Zur Anatomie der vogel-cochlea unter nat{ü}rlichen bedingungen. *Biol. Zent. Bl.* 79, 607–625.

Sherry, D. F. (2006). Neuroecology. *Annu. Rev. Psychol.* 57, 167–197. doi: 10.1146/annurev.psych.56.091103.070324

Shimizu, T., and Karten, H. (1991). "Central visual pathways in reptiles and birds: evolution of the visual system," in *Vision and Visual Dysfunction, Vol. 2: Evolution of the Eye and Visual System*, eds J. Cronly-Dillon and R. Gregory (London: Macmillan Press), 421–441.

Shimizu, T., and Karten, H. J. (1993). "The avian visual system and the evolution of the neocortex," in *Vision, Brain and Behavior in Birds*, eds P. Zeigler and H.-J. Bischof (Cambridge, MA: MIT Press), 103–114.

Shortess, G., and Klose, E. (1977). Effects of lesions involving efferent fibers to the retina in pigeons (*Columba livia*). *Physiol. Behav.* 18, 409–414. doi: 10.1016/0031-9384(77)90252-9

Silver, R., and Witkovsky, P. (1973). Functional characteristics of single units in the spinal trigeminal nucleus of the pigeon. *Brain Behav. Evol.* 8, 287–303. doi: 10.1159/000124359

Simpson, J. (1984). The accessory optic system. *Annu. Rev. Neurosci.* 7, 13–41. doi: 10.1146/annurev.ne.07.030184.000305

Simpson, J. I., Leonard, C. S., and Soodak, R. E. (1988). The accessory optic system of rabbit. II. Spatial organization of direction selectivity. *J. Neurophysiol.* 60, 2055–2072.

Soares, D., and Niemiller, M. L. (2013). Sensory adaptations of fishes to subterranean environments. *Bioscience* 63, 274–283. doi: 10.1525/bio.2013.63.4.7

Sol, D., Bacher, S., Reader, S. M., and Lefebvre, L. (2008). Brain size predicts the success of mammal species introduced into novel environments. *Am. Nat.* 172(Suppl.), S63–S71. doi: 10.1086/588304

Sol, D., Székely, T., Liker, A., and Lefebvre, L. (2007). Big-brained birds survive better in nature. *Proc. Biol. Sci.* 274, 763–769. doi: 10.1098/rspb.2006.3765

Stingelin, W. (1965). *Qualitative und quantitative Untersuchungen an Kerngebieten der Medulla oblongata bei Vögeln*. Basel: John Wiley & Sons.

Striedter, G. F. (2005). *Principles of Brain Evolution*. Sunderland: Sinauer Associates.

Sun, H., and Frost, B. J. (1998). Computation of different optical variables of looming objects in pigeon nucleus rotundus neurons. *Nat. Neurosci.* 1, 296–303. doi: 10.1038/1110

Takahashi, T. T. (2010). How the owl tracks its prey–II. *J. Exp. Biol.* 213, 3399–3408. doi: 10.1242/jeb.031195

Takahashi, T. T., and Konishi, M. (1988a). Projections of nucleus angularis and nucleus laminaris to the lateral lemniscal nuclear complex of the barn owl. *J. Comp. Neurol.* 274, 212–238. doi: 10.1002/cne.902740207

Takahashi, T. T., and Konishi, M. (1988b). Projections of the cochlear nuclei and nucleus laminaris to the inferior colliculus of the barn owl. *J. Comp. Neurol.* 274, 190–211. doi: 10.1002/cne.902740206

Takahashi, T. T., Bala, A. D. S., Spitzer, M. W., Euston, D. R., Spezio, M. L., and Keller, C. H. (2003). The synthesis and use of the owl's auditory space map. *Biol. Cybern.* 89, 378–387. doi: 10.1007/s00422-003-0443-5

Takahashi, T., Moiseff, A., and Konishi, M. (1984). Time and intensity cues are processed independently in the auditory system of the owl. *J. Neurosci.* 4, 1781–1786.

Thompson, C. K., and Brenowitz, E. A. (2005). Seasonal change in neuron size and spacing but not neuronal recruitment in a basal ganglia nucleus in the avian song control system. *J. Comp. Neurol.* 481, 276–283. doi: 10.1002/cne.20381

Tömböl, T., Alpár, A., Eyre, M. D., and Németh, A. (2006). Topographical organisation of projections from the nucleus isthmi magnocellularis to the optic tectum of the chick brain. *Anat. Embryol. (Berl.)* 211, 119–128. doi: 10.1007/s00429-005-0060-2

Tramontin, A. D., Hartman, V. N., and Brenowitz, E. A. (2000). Breeding conditions induce rapid and sequential growth in adult avian song control circuits: a model of seasonal plasticity in the brain. *J. Neurosci.* 20, 854–861.

Uchiyama, H. (1989). Centrifugal pathways to the retina: influence of the optic tectum. *Vis. Neurosci.* 3, 183–206. doi: 10.1017/S0952523800009950

Uchiyama, H., Nakamura, S., and Imazono, T. (1998). Long-range competition among the neurons projecting centrifugally to the quail retina. *Vis. Neurosci.* 15, 417–423. doi: 10.1017/S0952523898153026

Van Dijk, T. (1973). A comparative study of hearing in owls of the family strigidae. *Netherlands J. Zool.* 23, 131–167. doi: 10.1163/002829673X00120

Volman, S. F., and Konishi, M. (1990). Comparative physiology of sound localization in four species of owls (Part 2 of 2). *Brain Behav. Evol.* 36, 206–215. doi: 10.1159/000316083

Wagner, H., and Frost, B. (1993). Disparity-sensitive cells in the owl have a characteristic disparity. *Nature* 364, 796–798. doi: 10.1038/364796a0

Wallman, J., and Pettigrew, J. (1985). Conjugate and disjunctive saccades in two avian species with contrasting oculomotor strategies. *J. Neurosci.* 5, 1418–1428.

Wang, R., Chen, C.-C., Hara, E., Rivas, M. V., Roulhac, P. L., Howard, J. T., et al. (2015). Convergent differential regulation of SLIT-ROBO axon guidance genes in the brains of vocal learners. *J. Comp. Neurol.* 523, 892–906. doi: 10.1002/cne.23719

Wang, Y. C., Jiang, S., and Frost, B. J. (1993). Visual processing in pigeon nucleus rotundus: luminance, color, motion, and looming subdivisions. *Vis. Neurosci.* 10, 21–30. doi: 10.1017/S0952523800003199

Wang, Y., Luksch, H., Brecha, N. C., and Karten, H. J. (2006). Columnar projections from the cholinergic nucleus isthmi to the optic tectum in chicks (*Gallus gallus*): a possible substrate for synchronizing tectal channels. *J. Comp. Neurol.* 494, 7–35. doi: 10.1002/cne.20821

Wang, Y., Major, D. E., and Karten, H. J. (2004). Morphology and connections of nucleus isthmi pars magnocellularis in chicks (*Gallus gallus*). *J. Comp. Neurol.* 469, 275–297. doi: 10.1002/cne.11007

Ward, R., Repérant, J., and Miceli, D. (1991). "The centrifugal visual system: what can comparative studies tell us about its evolution and possible function?," in *The Changing Visual System*, eds P. Bagnoli and W. Hodos (New York, NY: Plenum Press), 61–76.

Warrick, D. R., Tobalske, B. W., and Powers, D. R. (2005). Aerodynamics of the hovering hummingbird. *Nature* 435, 1094–1097. doi: 10.1038/nature03647

Weidner, C., Repérant, J., Desroches, A.-M., Miceli, D., and Vesselkin, N. P. (1987). Nuclear origin of the centrifugal visual pathway in birds of prey. *Brain Res.* 436, 153–160. doi: 10.1016/0006-8993(87)91568-X

Whitchurch, E. A., and Takahashi, T. T. (2006). Combined auditory and visual stimuli facilitate head saccades in the barn owl (*Tyto alba*). *J. Neurophysiol.* 96, 730–745. doi: 10.1152/jn.00072.2006

Wild, J. M. (1981). Identification and localization of the motor nuclei and sensory projections of the glossopharyngeal, vagus, and hypoglossal nerves of the cockatoo (*Cacatua roseicapilla*), Cacatuidae. *J. Comp. Neurol.* 203, 351–377. doi: 10.1002/cne.902030304

Wild, J. M. (1997). The avian somatosensory system: the pathway from wing to Wulst in a passerine (*Chloris chloris*). *Brain Res.* 759, 122–134. doi: 10.1016/S0006-8993(97)00253-9

Wild, J. M., and Farabaugh, S. M. (1996). Organization of afferent and efferent projections of the nucleus basalis prosencephali in a passerine, *Taeniopygia guttata*. *J. Comp. Neurol.* 365, 306–328.

Wild, J. M., Arends, J. J., and Zeigler, H. P. (1985). Telencephalic connections of the trigeminal system in the pigeon (*Columba livia*): a trigeminal sensorimotor circuit. *J. Comp. Neurol.* 234, 441–464. doi: 10.1002/cne.902340404

Wilson, M., and Lindstrom, S. H. (2011). What the bird's brain tells the bird's eye: the function of descending input to the avian retina. *Vis. Neurosci.* 28, 337–350. doi: 10.1017/S0952523811000022

Wilson, P. (1980). The organization of the visual hyperstriatum in the domestic chick. II. Receptive field properties of single units. *Brain Res.* 188, 333–345. doi: 10.1016/0006-8993(80)90035-9

Wilson, V. J., and Melvill Jones, G. (1979). *Mammalian Vestibular Physiology*. New York, NY: Plenum.

Winterson, B. J., and Brauth, S. E. (1985). Direction-selective single units in the nucleus lentiformis mesencephali of the pigeon (*Columba livia*). *Exp. Brain Res.* 60, 215–226. doi: 10.1007/BF00235916

Wirthlin, M., Lovell, P. V., Jarvis, E. D., and Mello, C., V (2014). Comparative genomics reveals molecular features unique to the songbird lineage. *BMC Genomics* 15:1082. doi: 10.1186/1471-2164-15-1082

Wise, L. Z., Frost, B. J., and Shaver, S. W. (1988). The representation of sound frequency and space in the mid brain of the Saw-whet Owl. *Soc. Neurosci. Abstr.* 14, 1095.

Witkovsky, P., Zeigler, H. P., and Silver, R. (1973). The nucleus basalis of the pigeon: a single-unit analysis. *J. Comp. Neurol.* 147, 119–128. doi: 10.1002/cne.901470106

Wolf-Oberhollenzer, F. (1987). A study of the centrifugal projections to the pigeon retina using two fluorescent markers. *Neurosci. Lett.* 73, 16–20. doi: 10.1016/0304-3940(87)90023-1

Woodson, W., Shimizu, T., Wild, J. M., Schimke, J., Cox, K., and Karten, H. J. (1995). Centrifugal projections upon the retina: an anterograde tracing study in the pigeon (*Columba livia*). *J. Comp. Neurol.* 362, 489–509. doi: 10.1002/cne.903620405

Wylie, D. R. W., and Crowder, N. A. (2000). Spatiotemporal properties of fast and slow neurons in the pretectal nucleus lentiformis mesencephali in pigeons. *J. Neurophysiol.* 84, 2529–2540.

Wylie, D. R., Kolominsky, J., Graham, D. J., Lisney, T. J., and Gutierrez-Ibanez, C. (2014). Retinal projection to the pretectal nucleus lentiformis mesencephali in pigeons (*Columba livia*). *J. Comp. Neurol.* 522, 3928–3942. doi: 10.1002/cne.23649

Wylie, D. R., Shaver, S. W., and Frost, B. J. (1994). The visual response properties of neurons in the nucleus of the basal optic root of the northern saw-whet owl (*Aegolius acadicus*). *Brain Behav. Evol.* 43, 15–25. doi: 10.1159/000113620

Xiao, Q., and Frost, B. J. (2009). Looming responses of telencephalic neurons in the pigeon are modulated by optic flow. *Brain Res.* 1305, 40–46. doi: 10.1016/j.brainres.2009.10.008

Xiao, Q., Li, D.-P., and Wang, S.-R. (2006). Looming-sensitive responses and receptive field organization of telencephalic neurons in the pigeon. *Brain Res. Bull.* 68, 322–328. doi: 10.1016/j.brainresbull.2005.09.003

Zeigler, H. P., and Bischof, H.-J. (1993). *Vision, Brain, and Behavior in Birds*. Cambridge, MA: MIT Press.

Zeigler, H. P., and Witkovsky, P. (1968). The main sensory trigeminal nucleus in the pigeon: a single-unit analysis. *J. Comp. Neurol.* 134, 255–263. doi: 10.1002/cne.901340302

Zweers, G. A., and Gerritsen, A. F. C. (1996). Transitions from pecking to probing mechanisms in waders. *Netherlands J. Zool.* 47, 161–208. doi: 10.1163/156854297X00166

Zweers, G. A., Berkhoudt, H., and Vanden Berge, J. C. (1994). "Behavioral mechanisms of avian feeding," in *Biomechanics of Feeding in Vertebrates*, eds V. L. Bels, M. Chardon, and P. van de Walle (Berlin: Springer), 241–279.

Zweers, G. A., Gerritsen, A. F. C., and van Kranenburg-Voogd, P. J. (1977). *Mechanics of Feeding of the Mallard (Anas platyrhynchos L.; Aves, Anseriformes): The Lingual Apparatus and the Suction-pressure Pump Mechanism of Straining*. Basel: Karger Publishers.

Conflict of Interest Statement: The editor Jorge Mpodozis declares that, despite having collaborated on an article with authors Cristian Gutiérrez-Ibáñez and Andrew Iwaniuk in 2013, the review was conducted objectively. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

HYPOTHESIS AND THEORY
published: 27 October 2015
doi: 10.3389/fnins.2015.00402

Olfaction, navigation, and the origin of isocortex

Francisco Aboitiz[1]* *and Juan F. Montiel*[2,3]

[1] *Departamento de Psiquiatría, Escuela de Medicina, Centro Interdisciplinario de Neurociencia, Pontificia Universidad Católica de Chile, Santiago, Chile,* [2] *Facultad de Medicina, Centro de Investigación Biomédica, Universidad Diego Portales, Santiago, Chile,* [3] *MRC Functional Genomics Unit, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK*

There are remarkable similarities between the brains of mammals and birds in terms of microcircuit architecture, despite obvious differences in gross morphology and development. While in reptiles and birds the most expanding component (the dorsal ventricular ridge) displays an overall nuclear shape and derives from the lateral and ventral pallium, in mammals a dorsal pallial, six-layered isocortex shows the most remarkable elaboration. Regardless of discussions about possible homologies between mammalian and avian brains, a main question remains in explaining the emergence of the mammalian isocortex, because it represents a unique phenotype across amniotes. In this article, we propose that the origin of the isocortex was driven by behavioral adaptations involving olfactory driven goal-directed and navigating behaviors. These adaptations were linked with increasing sensory development, which provided selective pressure for the expansion of the dorsal pallium. The latter appeared as an interface in olfactory-hippocampal networks, contributing somatosensory information for navigating behavior. Sensory input from other modalities like vision and audition were subsequently recruited into this expanding region, contributing to multimodal associative networks.

Keywords: isocortical evolution, plasticity, olfaction, hippocampus

OPEN ACCESS

Edited by:
Lisa M. Renzi,
The University of Georgia, USA

Reviewed by:
Christian Leibold,
Ludwig Maximilians University, Germany
Thomas Mueller,
Kansas State University, USA

***Correspondence:**
Francisco Aboitiz
faboitiz@puc.cl

Specialty section:
This article was submitted to Evolutionary Psychology and Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *16 July 2015*
Accepted: *12 October 2015*
Published: *27 October 2015*

Citation:
Aboitiz F and Montiel JF (2015) Olfaction, navigation, and the origin of isocortex. Front. Neurosci. 9:402. doi: 10.3389/fnins.2015.00402

INTRODUCTION

Mammals are the descendants of one of the two main amniote clades that colonized the ground by developing an egg that could be laid outside of water. This spectacular innovation yielded two lineages that diverged very early and underwent parallel histories since the late Carboniferous period, some 300 million mya. One of these is the stem reptile, giving rise to all known reptiles and birds (together called sauropsids); and the other is represented by the synapsid or mammal-like reptile. At some point in the Cretaceous, both groups underwent a parallel tendency to increase brain size, in the two most successful clades of each branch: mammals and birds. Beside the increase in brain size, both groups developed highly divergent overall brain anatomies. Sauropsids have a nuclear-shaped dorsal ventricular ridge (DVR) and mammals display a six-layered isocortex. Intriguingly, while the gross brain morphology is quite different in these two taxa, studies in the last 50 years have found significant similarities in brain organization and behavior in the two groups (Wang et al., 2010; Ahumada-Galleguillos et al., 2015; Calabrese and Woolley, 2015). The observed disparity between gross morphology and connectivity has raised an agitated controversy regarding the origins and evolution of such patterns (Aboitiz and Montiel, 2007, 2012). Yet, the most important question remains, namely why only mammals evolved a laminated isocortex. In two companion articles to this one (Bosman and Aboitiz, 2015; Montiel and Aboitiz, 2015),

as well as in previous articles (Aboitiz et al., 2003; Aboitiz, 2011; Aboitiz and Zamorano, 2013), we have elaborated an evolutionary developmental hypothesis for the unique laminar development and connectivity of the isocortex. Instead, in this paper we will discuss the selective processes that participated in generating these two divergent phenotypes, particularly that of the mammalian isocortex. Basically, we will argue that the observed differences in gross anatomical structures between birds and mammals are the result of contingent adaptations in lifestyle, reflected in the organization of sensory and motor systems, which drove mammalian brain development away from a more conservative developmental trend as is found in sauropsids. Nonetheless, this condition was no obstacle for the parallel development of highly similar functional circuits and behaviors in both lineages (Güntürkün, 2012; Clayton and Emery, 2015).

THE ECOLOGICAL CONTEXT

The main question we address here is what ecological and adaptive circumstances selected for the origin of the mammalian brain. To answer this, it is necessary to analyze the ecological niche these animals created, and consider the behavioral and sensory adaptations these animals developed. Basically, the special features that characterize the isocortex are the consequence of specific sensory and behavioral adaptations that in turn selected for developmental modulations in the telencephalon. Initially, these modifications included mainly olfaction and touch, which were involved in linear navigation behavior. As mammals invaded new ecological niches, vision and audition provided additional information about distance and location. This resulted in the development of the isocortex as a multimodal associative system that contributed to generate spatial maps of the environment.

Mesozoic Mammals

Mammals are descendant from cynodonts, a small-sized, omnivorous synapsid lineage originating in the late Permian (about 260 mya), which gave rise to the first mammal-like animals in the mid Triassic (230 mya). The first mammals were a diverse group termed mammaliamorphs (miniaturized mammals such as probainognathids and tritylodontids), which were replaced by mammaliaforms (including moganucodonts and docodonts). Finally, the crown or modern mammals appeared, including fossil triconodontids, multituberculates, and the extant monotremes and therians (marsupials and placentals, or eutherians; Kielan-Jaworowska et al., 2004; Luo, 2007; Rowe and Shepherd, 2015; see **Figure 1**). The radiation of these early mammalian clades took place quite early and lasted through the Jurassic and Cretaceous, but only the monotremes and therians appear to have lasted beyond the Cretaceous. Thus, contrary to common belief, early mammals underwent a successful adaptive radiation throughout the age of dinosaurs (Luo, 2007).

The origin of mammals was marked by several anatomical and physiological innovations that began with the formation of a secondary palate in cynodonts. This character permitted a separation of the nasal structures from the mouth, generating a moistened air chamber for olfaction. Furthermore, the secondary palate is associated with profound changes in dental structure for mastication, in the tongue for swallowing and in the thoracic cavity that developed a diaphragm for active respiration. The capacity for smell increased, influencing exploratory behavior and providing the possibility for retronasal smell and the generation of complex flavor sensations. These innovations were concomitant with a modest brain expansion in early mammals, as exemplified by *Morganucodon*, a late Triassic-early Jurassic mammaliaform, in which relative brain size was about 50% larger than that of basal cynodonts (Rowe et al., 2011; Rowe and Shepherd, 2015). This increase in brain size is mostly accounted for by an expansion of the olfactory bulb and olfactory cortex, although there is also a larger cortical area and an expanded cerebellum. Moreover, in *Castorocauda*, a mid-Jurassic beaver-tailed mammaliaform, there is evidence of pelt and presumably a somatosensory region in the presumptive isocortex (Rowe et al., 2011). This may have been accompanied by the formation of secretory glands, the production of milk and the acquisition of full homeothermy. An additional increase in brain growth occurred in *Hadrocodium* (a small, early crown mammal some 3 cm long, from the early Jurassic in China), where again most growth was due to the olfactory bulbs and olfactory cortex. In *Hadrocodium*, there is detachment of the middle ear ossicles from the jaw apparatus, presumably due to expansion of the olfactory cortex (Rowe et al., 2011; Rowe and Shepherd, 2015). However, this may not mean a great increase in auditory sensitivity as the cochlea remained short, as in cynodonts. *Hadrocodium* still lacked ossified turbinals (intricate spongy nasal bones that warm and moisten the air as it enters the lungs), and had a primitive chewing and swallowing system. Full ossification of the turbinal bones, that allowed expansion of the olfactory epithelium, is only seen in more advanced crown mammals.

We will now address the evolution of sensory organs and their central projections in early mammals, to provide a picture of their presumed behavior and the selective pressures that were acting on these sensory systems. We propose that olfaction (and touch) played a dominant role in the earliest mammals, participating in linear navigation. In later stages, other senses (together with increasing motor control) contributed to the development of a primitive isocortex containing multimodal, map-like representations of space.

Adaptations to Nocturnal Behavior

It is generally agreed that early mammals underwent a "nocturnal bottleneck" (Walls, 1942), which is consistent with the presumed burrowing behavior of cynodonts. However, nocturnal adaptations most likely arose in the ancestral synapsids some 100 million years before the appearance of the earliest mammals (Angielczyk and Schmitz, 2014). Ample comparative evidence supports the nocturnal hypothesis, including the paucity of chromatic receptor cells and visual pigments in the retina, the night-adapted eye morphology (bearing a large cornea to maximize visual input at the expense of acuity, as well as a tapetum lucidum), and the loss of the corneal UV filter in the majority of extant mammals (Heesy and Hall, 2010; Hall et al., 2012; Gerkema et al., 2013). Another character common in nocturnal animals is binocularity, which is assumed

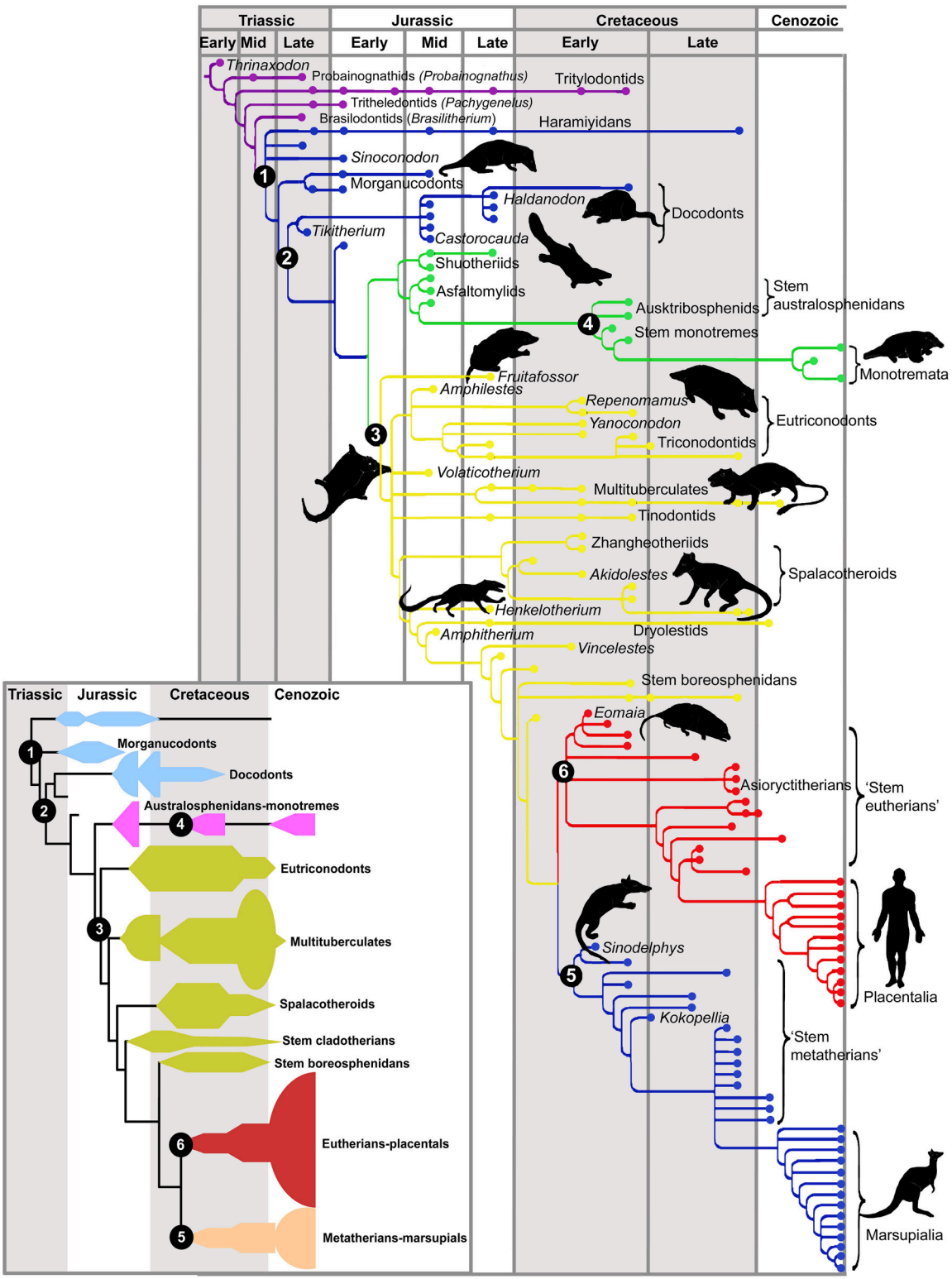


FIGURE 1 | Phylogeny of fossil mammals. Critical phylogenetic nodes are shown in numbers. The inset provides a summary diagram of the different clades. Cynodonts are shown in purple. Node (1, blue) mammaliamorphs, a group of advanced cynodonts; (2, also blue) mammaliaforms. The common ancestor of modern mammals (crown mammals) is shown at the base of the green tree. This line gives rise to most mesozoic mammals (3, yellow) and to monotremes (4, green). The common ancestor of therians (marsupials and placentals) stays at the base of (5, blue) marsupials or metatherians and (6, red) placentals or eutherians. Note the dramatic extinction of mammalian lineages at the end of the Cretaceous, concomitant with the extinction of the dinosaurs. With permission from Luo (2007).

to provide benefits in light and contrast sensitivity, but not necessarily in depth perception (Vega-Zuniga et al., 2013). Note that binocularity is concomitant with growth of the direct retino-thalamic visual pathway (as opposed to the alternative visual pathway that relay in the midbrain before reaching the thalamus, which is the more developed in sauropsids), in both birds and mammals (Heesy and Hall, 2010; Gaillard et al., 2013). Noticeably, the chromatine structure of mammalian rod photoreceptors differs between diurnal and nocturnal mammals, with nocturnal mammals displaying a unique inverted pattern with dense heterochromatin condensed in the nucleus' center, and euchromatin in the periphery, while diurnal mammals show the reverse pattern (Solovei et al., 2009). The nocturnal, inverted pattern generates a geometry that works as a collecting lens that maximizes light input into the receptor's light sensitive outer segment.

It is extremely interesting to compare this pattern with non-mammalian species to elucidate a possible evolutionary pattern [note that anthropoid primates are an exception to many of the above adaptations as they have re-evolved color vision (Gerkema et al., 2013)]. In these conditions, other senses, notably olfaction, but also somatosensation and to a lesser extent audition, underwent a compensatory development, which we suggest produced a dramatic change in the lifestyle of the early cynodonts. In later stages, as mammals recolonized diurnal niches, vision (and audition) contributed a significant input to behavioral orientation, perhaps concomitant with expansion of the isocortex.

Audition and Mastication

While the emergence of a tympanic ear took place several times in amphibians, stem reptiles and mammal-like therapsids (Grothe and Pecka, 2014), the emergence of the middle ear ossicles and the consequent amplification of the auditory capacity represent critical acquisitions in mammalian evolution. This process began with a series of modifications of the jaw apparatus in relation to new feeding habits and more elaborate dentition. This condition resulted in the elaboration of the dentary bone in the mandible, which began to make contact with the squamosal bone in the cranium in primitive mammaliamorphs like *Pachygenelus* (a small tritylodont cynodont from the early Jurassic), and gradually replaced the ancestral quadrate-articular jaw joint that is seen in reptiles and mammal-like reptiles (Luo et al., 2001; Luo, 2007). The ancestral quadrate and articular bones became released, and the articular from the lower jaw became the mammalian malleus. The quadrate from the upper jaw evolved into the incus, and attached to the stapes via a stapedial process that appears for the first time in *Brasilitherium* (a Triassic cynodont from Brazil; Luo, 2007). The evolution of the middle ear was a gradual and mosaic process, showing many convergences and divergences in different lineages that began some 200 million years ago (Luo et al., 2001; Luo, 2007). Rowe (1996a,b) reported that detachment of the middle ear ossicles was initially associated with an increase in brain size in fossils like *Triconodon* (a late Jurassic triconodontid, about the size of a domestic cat) and *Hadrocodium* (mentioned above). Subsequent evidence showed that in other early mammals like *Repenomanus* (a carnivore triconodont from the early Cretaceous of China) the reverse is the case: they bear narrow braincases associated with detachment of the middle ear ossicles, indicating that more likely, the acquisition of the middle ear predated the increase in brain size in early mammals (Wang et al., 2001). Another hypothesis is that the volumetric expansion of the olfactory cortex in the lateral hemisphere of *Hadrocodium* forced the detachment of the middle ear ossicles from the jaw articulation (Rowe and Shepherd, 2015). However, the fossil *Yanocodon* (a burrowing triconodont from the early Cretaceous of China) shows increased brain size and ossicles still attached to the mandible (Luo, 2007). Nonetheless, Rowe and Shepherd (2015) interpret this unique fossil specimen as a juvenile, reminiscent of young marsupials, in which the ossicles are attached to the jaw during early development, and are released in later stages.

The elaboration of a coiled cochlea, allowing detection of high frequency sounds (above 10 KHz), took place much later, some 60 million years ago in therian mammals with modern brain sizes (Manley, 2012, 2013). Enlargement of the cochlea occurred concomitant with the expansion of the auditory epithelium or organ of Corti. Furthermore, the elaboration of the cochlea most likely has been accompanied by the acquisition and gradual elaboration of prestin-dependent electromotility of hair cells in therians and placentals, respectively (Liu et al., 2012). As in reptiles, the monotreme auditory epithelium is separated in two components: the basilar papilla and the lagenar macula, while therians have fused both surfaces in the organ of Corti (Fritzsch et al., 2013). More interestingly, although monotremes have an incompletely curved cochlea, it shows some mammalian features like a separation of inner and outer cells in the organ of Corti and nonlinear, cochlear amplification mechanisms that enhance auditory perception (Ashwell et al., 2014). Additional evidence for a mosaic evolution of the inner ear comes from the Jurassic mammal *Dryolestes*, which shows derived features of therian-like auditory cochlear innervation, but still has an uncoiled cochlea (Luo et al., 2011).

Together with increasing auditory discrimination and sensitivity to high frequency sounds, audition may have served a particular role in spatial orientation, by comparing the time differences between auditory inputs to each ear (determining azimuth of the sound source), and especially by processing the variations in the spectral cues associated with movement of the sound source and the direction of the pinnae (for which high frequency detection is relevant). An additional factor are the interaural level differences caused by sound crossing through the head or the body to reach the ear contralateral to the sound source (Heffner and Heffner, 1992a; Grothe and Pecka, 2014). While sauropsids tend to rely mostly on interaural time differences for sound localization, mammals also use frequency analysis to detect source movement and sound distortion processes to obtain spatial information, for which high frequency detection is highly relevant (Grothe and Pecka, 2014). Furthermore, auditory localization is tightly correlated with the control of eye movements (Heffner and Heffner, 1992b).

Although much of sound localization takes place subcortically, it is possible that the auditory cortex plays a role in localization of sound sources as well (Lee and Middlebrooks,

2011). However, it seems that the role of the auditory cortex in sound localization varies across mammals, as auditory cortex ablations tend to have little effect in rats but can have severe effects in cats, dogs, and monkeys (Kelly, 1980; Kelly and Kavanagh, 1986). We still do not know the extent to which auditory development contributed to the initial expansion of the isocortex, but having an efficient system to localize sounds may have provided benefits for establishing multimodal cognitive maps in the cortex and hippocampus.

The Somatosensory System and Exploratory Behavior

Another sensory system that has been considered relevant for the evolution of the mammalian brain is touch. Mammals have a skin devoid of scales, usually covered by hair and highly innervated with different types of mechanoreceptors. In the region of the mouth, hairs differentiate as sensory vibrissae that move back and forth; furthermore, in some cases the mouth and nose themselves become highly specialized sensorimotor organs. In mammaliamorphs there is evidence of an increased trigeminal sensory input for perioral tactile sensation, but also for mastication and the possible development of muscle spindles and joint receptors that control posture and movement, providing these animals a mammal-like gait (Rowe and Shepherd, 2015). Since there is some evidence of mammal-like skin in mammaliaforms, Rowe and Shepherd (2015) suggested that these animals already displayed a somatosensory or somatomotor cortex in their moderately enlarged brain.

Grant et al. (2013) described a similar "whiskering" behavior in marsupials and rodents. This matches similarities in the anatomical arrangements of the vibrissal musculature, although there was a more elaborate whiskering function in rodents. Unfortunately, extant monotremes bear a derived beak-shaped mouth and may not be useful as models of early mammalian oral behavior. Vibrissae and other somatosensory oral structures can be used in different forms of tactile discrimination (Guic-Robles et al., 1989, 1992), but importantly they also participate in localizing and tracking objects (Krupa et al., 2001; Ahissar and Knutsen, 2008; Knutsen et al., 2008), as well as in orienting behavior (Hartmann and Bower, 2001). In addition to these specializations, increasing forepaw control and dexterity due to the elaboration of descending tracts from the pallium and the eventual elaboration of a corticospinal tract to the brainstem was very likely a positive factor in the generation of exploratory behavior and navigational capacities (Aboitiz and Montiel, 2007, 2012; Rowe and Shepherd, 2015). This points to a cooperative interaction between the oral somatosensory and other sensory and motor systems in spatial orientation in early mammals. Finally, more sensitive skin may have had important effects on the social behavior of early mammals, again in co-evolution with olfactory and pheromonal signals (Porter, 2004; see below). In this context, Lenschow and Brecht (2015) recently demonstrated that social contact evokes a strong anticipatory depolarization and membrane fluctuations in the barrel cortex of rats (representing the sensory input of whiskers), which are different from those seen in free whiskering behavior and are not triggered by non-conspecific stimuli.

Olfaction in Early Mammals

Olfaction is the most expansive sense in mammals, with an olfactory receptor gene family that makes up 1% of the mammalian genome, and is some 10-fold larger than in any other vertebrate group (Niimura, 2009; Hoover, 2010). Furthermore, by virtue of their diaphragm-based respiration and the development of a secondary palate in their mouth, mammals are able to actively sniff the air in search of volatile substances, and have accordingly developed the nasal turbinals that facilitated expansion of the olfactory epithelium. This design also allows the generation of retronasal smelling, which combines with taste information from the mouth, producing the complex sense of flavor (Shepherd, 2007; Hoover, 2010). Unfortunately, the effects of this condition in the evolution of taste, and the role of taste in mammalian evolution, are subjects of great interest but there is as yet little comparative evidence. In the neocortex, gustatory representation lies on the insula and the frontal lobe. These regions also process internal sensations and may have benefited from neural expansion in the lateral-frontal pallium, associated with the development of endothermy and more sophisticated homeostatic functions (Smart, 2008).

Returning to olfaction, the early cynodont *Brasilitherium* already displayed partial ossification of the nasal septum and expansion of the posterior nasal cavity, as seen in computerized tomography imaging (Ruf et al., 2014). However, the relative sizes of olfactory structures started a dramatic expansion in mammaliaforms, together with a stepwise amplification of brain size. Rowe et al. (2011) performed X-ray computer tomography on a series of Cretaceous cynodont, mammaliaform and early mammalian skulls, unveiling an association between increasing absolute size of turbinal bones, olfactory bulbs and olfactory cortex on the one hand, and absolute brain size on the other. Rowe et al. (2011) largely attributed this finding to the amplification of olfactive capacity, but also highlighted the elaboration of somatosensory and auditory processing as concomitant factors. One important function served by the olfactory system is olfactory discrimination, both ortho- or retronasal. Shepherd and others have argued that the olfactory bulb is capable of generating an "odor image," while the olfactory cortex develops "olfactory objects" much like what is found in different stages of visual processing (Shepherd, 2007; Rowe and Shepherd, 2015). Importantly, this implies that the olfactory cortex is functionally equivalent to a higher-order, associative cortical area rather than to a primary sensory area.

Comparative Development of Mammalian Olfactory Cortex

Notably, olfactory and olfactory-related brain regions do not show conservative allometric growth in different species. In mammals, all prosencephalic (anterior brain) components—except limbic structures like the olfactory cortex and hippocampus—follow a general allometric rule in which the growth relations between components are highly constrained, within a two or three-fold range, which may give space for ecological adaptations (Barton et al., 1995; Yopak et al., 2010). On the other hand, olfactory structures and the hippocampus correlate positively between them, but their relative sizes show

a general inverse relation with isocortical growth. That is, although they may increase in absolute size, this increase is far more modest than the other brain structures (Reep et al., 2007). Furthermore, Jacobs (2012) claimed that the relative size of olfactory systems depends on the predictability of the food sources in different species. Animals that scan their environment to obtain prey or that have plenty of food available need little navigational capacities and score low in relative size of olfactory components, while species that have to search for their prey tend to score high in olfactory structures. Moreover, it is one thing to find one's source of food, it is another to capture it. Thus, animals like carnivores, which have to develop complex strategies to chase their prey, display both relatively large olfactory structures and a large isocortex, while simians that have no difficulty in obtaining food but have a complex, visually oriented social life have a relatively small olfactory system and a large isocortex (see also Gilad et al., 2004). On the other hand, microbats have both a small olfactory system and a small neocortex, while prosimians and insectivores have large olfactory components and a small isocortex in relation to total brain size. Jacobs (2012) asserts that prosimians and insectivores, with a large olfactory cortex and a small isocortex, better resemble the condition of ancestral mammals.

Olfaction in Social and Maternal Behavior

Social and maternal behaviors were also significant innovations in early mammalian evolution, and deserve to be discussed in this context. Considering that early mammals had nocturnal habits and a significant reduction of the visual system, a large part of their social signaling system may have relied on olfactory and pheromone cues. Chemical signals are involved in territorial marking, individual identification and sexual behavior, among other functions, which may have been quite important for early mammalian behavior. The olfactory system in mammals is importantly connected to areas involved in social reward, modulating neuroendocrine functions that facilitate social learning, and maternal behavior (Broad et al., 2006; Sanchez-Andrade and Kendrick, 2009). The accessory olfactory bulb can detect chemical signals like proteins of the major histocompatibility complex or urinary proteins that not only permit recognizing individuals, but also their genetic relatedness (Brennan and Kendrick, 2006). Interestingly, mammalian adult olfactory neurogenesis in rats has been found to depend on reproductive behavior (Feierstein, 2012). Furthermore, the social behavior modulators oxytocin and vasopressin are expressed in the main and accessory olfactory bulbs and participate in the formation of short-term social odor memories (Wacker and Ludwig, 2012).

Pheromones and olfactory cues may be critical for mammalian maternal behavior through modulation of the neuroendocrine system (Lévy et al., 2004; Sanchez-Andrade and Kendrick, 2009; Schaal, 2010). Milk secretion is triggered by oxytocin in response to the sight, sound and smell of human babies (Leng et al., 2005). While not lactating, female rodents find the odor of pups aversive, while after parturition and during lactation, the same stimulus results in a potent approaching trigger. Furthermore, in rodents mother-child individual recognition seems to depend exclusively on the main olfactory system, and the main olfactory bulb undergoes profound synaptic changes with exposure to offspring odors at parturition, contributing to the memorization of odors and long-term maternal behavior (Lévy et al., 2004). Olfaction is perhaps more important to puppies, who have to search for the milk sources in their mother's bellies. In therian mammals, chemical signals emanating from mammary glands are key for arousal, attraction and orienting behavior to the mother and to reach the milk sources (Raihani et al., 2009; Stevenson, 2009; Schaal, 2010). For example, rabbit kittens have shown specific nipple-search behavior in response to cues like the mammary pheromone (Schaal et al., 2003; Raihani et al., 2009). This may be considered as the earliest navigational function of olfaction in a newborn mammal. In addition, milk and belly secretions may have served as the first social signals secreted by early mammals, as abdominal odor cues are used by newborn mammals to distinguish between different adult conspecifics (Schaal et al., 2009).

Nonetheless, monotremes did not concentrate mammary glands and teats. Milk is produced from secretory glands located in their bellies, and this condition may be closer to that of early mammals. Moreover, monotremes start producing milk just after they lay the eggs, and not at the time newborns hatch (Enjapoori et al., 2014). One hypothesis claims that milk evolved from belly secretions that originally served to avoid dessication of the soft-shelled eggs laid by primitive mammals, resembling the condition of modern monotremes (Warren et al., 2008). Furthermore, monotreme milk contains antibacterial proteins that help protect the altricial newborns from pathogens (Enjapoori et al., 2014). Interestingly, the nutritious protein component of the milk, casein, is already present in the milk of monotremes, but these animals also express vitellogenin in their eggs to nourish the embryos before hatching. In therians, however, vitellogenin genes have been pseudogenized (inactivated by nonsense mutations) at the expense of evolving more copies of casein genes (Brawand et al., 2008). In living monotremes the olfactory system has been reported not to be functional at birth (Ashwell, 2012), perhaps implying that the active compound eliciting preferential orientation to milk sources is associated with the acquisition of nipples in therian mammals, or that extant monotremes lost this capacity in their evolution. The latter is plausible considering that they have a poorly developed olfactory system, perhaps at the expense of an increased electrosensory sensitivity that aids them in searching for food (Ashwell, 2013). Whether early mammals relied on navigational cues to find their mother and the milk sources is still unknown, but one can provisionally speculate that such was the case.

Olfactory Connections with the Hippocampus and Role in Navigation

Jacobs (2012) recently argued that more than as a sense involved in discriminating stimuli, olfaction works as a reference system for spatial navigation, guiding the animal to locate food sources, or mates (see also Eichenbaum, 1998). Furthermore, Jacobs (2012) suggested that the navigational properties of the olfactory system serve as scaffolding for the evolution of a parallel orientation map in the hippocampus. Despite some variations,

a hippocampal region associated with spatial orientation (Day et al., 1999, 2001; Rodríguez et al., 2002), and an important olfactory-hippocampal projection (Striedter, 2015; **Figure 2**), are conserved features of all amniotes. In rodents, the olfactory system connects with the hippocampus through the entorhinal cortex, which also forms extensive associative networks with other sensory modalities in the isocortex (Lynch, 1986; Haberly, 1990; **Figure 3**).

Hippocampal cells display a fine olfactory recognition capacity, and spatial and non-spatial (olfactory) responses segregate in alternating bands in the hippocampal region (Hampson et al., 1999). According to Eichenbaum (1998), more than participating in sensory discrimination, the hippocampus is critical for associating relationships between different odors and for associating odors with different situations. In this line, Vanderwolf (2001) observed in the rat strong oscillatory gamma

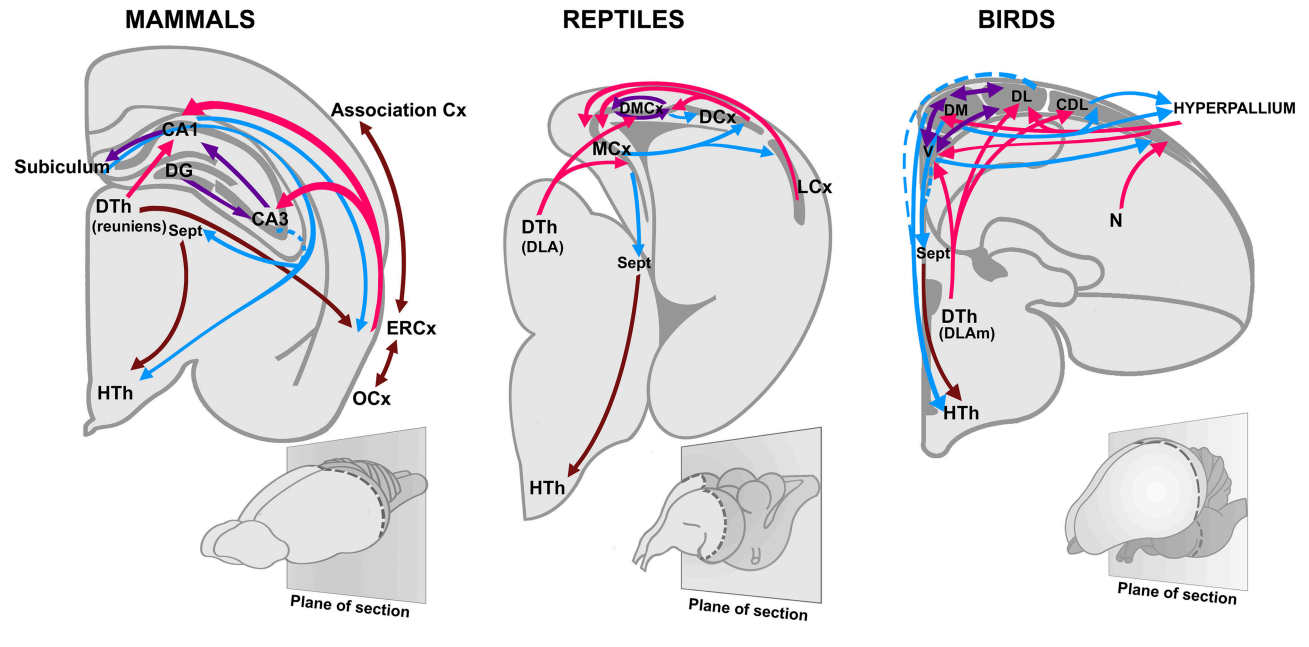


FIGURE 2 | Olfactory projections to the hippocampus in birds, reptiles, and mammals. Based on Striedter (2015), with permission. CA1, *Cornu Ammonis 1*; CA3, *Cornu Ammonis 3*; Cx, Cortex; DG, Dentate gyrus; DLA, Dorsolateral anterior nucleus; DLAm, medial part of the dorsolateral anterior nucleus; DTh, Dorsal thalamus; HTh, Hypothalamus; ERCx, Entorhinal cortex; DCx, Dorsal cortex; DL, dorsolateral division of the hippocampus; DM, dorsomedial division of the hippocampus; DMCx, Dorsomedial cortex; LCx, Lateral cortex; N, Nidopallium; MCx, Medial cortex; OCx, Olfactory cortex; Sept, Septum; V, ventral division of the hippocampus (also named V-shaped area).

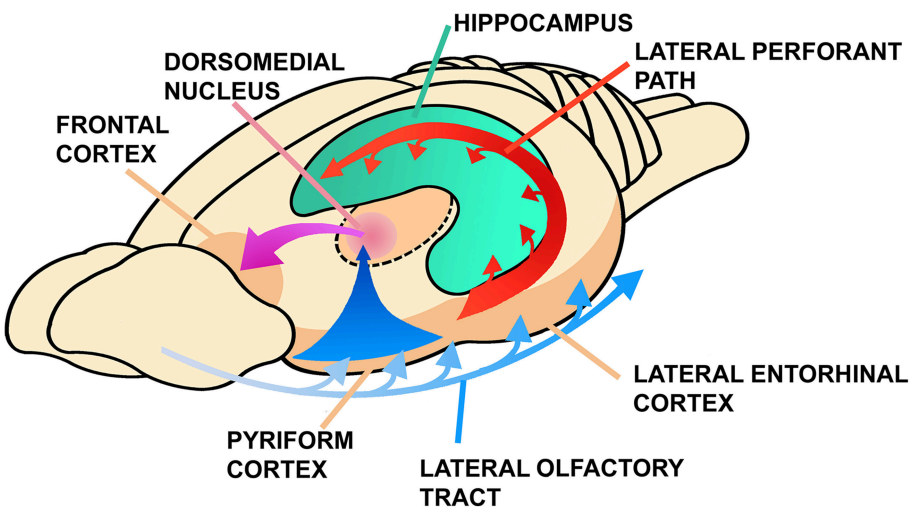


FIGURE 3 | Connections between the olfactory cortex, the hippocampus and the frontal cortex in mammals. Note the thalamic olfactory projection that is relayed to the frontal cortex. Modified from Lynch (1986), Figure 8A, pp. 28, ©1986 Massachusetts Institute of Technology, by permission of The MIT Press.

activity in the hippocampus, associated with active sniffing or by blowing odorants with a cannula under anesthesia, but not by stimulating other modalities in absence of movements. In line with our argument, Vanderwolf proposed that the hippocampus is basically an olfactory-motor system and the cognitive functions of this structure are a secondary acquisition. Furthermore, hippocampal "time cells" have been described that codify sequences of events that contribute to the formation of a spatio-temporal representation of the environment (MacDonald et al., 2011; Eichenbaum, 2014; Davachi and DuBrow, 2015). These representations are relayed to the prefrontal cortex to assimilate new memories in contextual networks in the process of memory consolidation (Preston and Eichenbaum, 2013).

Nonetheless, a more widespread interpretation of hippocampal function is that it contributes to establishing a Cartesian map of the space in which the animal navigates. Crucial elements for this function are the so-called "place cells" located in the hippocampal CA1 region, and the "grid cells" in the entorhinal cortex (Alme et al., 2014; Krupic et al., 2015). Particularly, the grid cells of the entorhinal cortex generate a bidimensional, grid-like periodic pattern as the animal moves in space (Fyhn et al., 2004; Hafting et al., 2005) and seem to be critical for spatial orientation. During navigation, information must be integrated between egocentric external cues and allocentric updates of current actions and position. Both kinds of signals are required to generate a time-independent, two-dimensional map during spatial exploration, provided by hippocampal place cells (Buzsáki, 2005). Particularly relevant in this context is information about head direction signals, conveying information from vestibular and motor systems, which provide a directional axis during exploration (Taube, 2007). These two types of input (external cues and body position and movement) are segregated in different regions of the entorhinal cortex, the dorsolateral entorhinal cortex providing information about external sensory cues, and the ventromedial entorhinal cortex conveying information about self-position and motion (Fyhn et al., 2004; Lisman, 2007). While the classical view is that entorhinal grid cells preferentially code information about the animal's self-motion (propioception), some evidence indicates that in some conditions, navigation is possible using only sensory landmarks (Poucet et al., 2013) These authors propose that bodily information is crucial for navigation, particularly in the dark, where grid cells are driven by self-motion inputs and in turn grid cells drive hippocampal place cells (Poucet et al., 2013).

Lastly, it is worth mentioning that the main regions in which adult neurogenesis occurs in mammals are precisely the olfactory bulb (Sanai et al., 2011) and the dentate gyrus of the hippocampus (Song et al., 2012). In this context, Sahay et al. (2011) have proposed that, despite their apparent differences, new granule cells in both structures reflect an adaptive mechanism to encode contextual information by modulating the process of pattern separation, that is, dissociating similar inputs on the basis of contextual information.

The Isocortex as a Multimodal Interface

Early mammals were probably nocturnal and fossorial, a condition in which internal cues like propioceptive information, together with sensory information from the olfactory and the somatosensory systems were crucial for linear navigation. In these conditions, orientation may have relied mainly on one-dimensional maps, coding for sequences of events in a time series (Buzsáki, 2005; Eichenbaum, 2014). However, as early mammals started to diversify and invaded diurnal niches, additional sensory inputs like vision and hearing, providing more detailed information on spatial relations, became increasingly important for generating accurate bidimensional and time-independent spatial maps.

Noticeably, the reptilian dorsal cortex (presumably a field homolog to the mammalian isocortex) can be compared in function and structure with the entorhinal and subicular cortices of mammals, which connect cortical and limbic areas with the hippocampus (Powers, 1990; Aboitiz et al., 2003; Aboitiz and Montiel, 2007; Butler et al., 2011). In this context, the early isocortex may have differentiated from the ancestral dorsal pallium (dorsal cortex in reptiles), as an interface between the olfactory cortex and the hippocampus to provide additional sensory information involved in navigation, perhaps initially somatosensory (Aboitiz et al., 2003; Aboitiz and Montiel, 2007). Supporting this proposal, the early mammaliaform *Castorocauda* may have had a rudimentary somatosensory cortex (Rowe et al., 2011), contributing to orientation behavior. Even if the reptilian dorsal cortex receives visual input, it does not participate in vision but rather in learning and memory (Powers, 1990). This may have been the case in early mammals, especially considering their nocturnal, burrowing habits. At later stages, the early expansion of the somatosensory region provided a substrate for the eventual strengthening of additional inputs like vision, especially when animals invaded diurnal niches.

In its origins, the expanding dorsal pallium of cynodonts and mammaliaforms displayed a predominantly tangential organization, with afferents running in the superficial marginal zone and contacting the apical dendrites of pyramidal neurons, as observed in the dorsal cortex of reptiles and the olfactory cortex of mammals and reptiles (Fournier et al., 2015; Naumann et al., 2015). This resembles the anatomical disposition of cortical afferents in small-brained, extant mammals (Nieuwenhuys, 1994). Furthermore, the neocortex has been claimed to display an intrinsic tangential organization, reminiscent of that of the olfactory cortex (for more details, see Shepherd, 2007, 2011; Bosman and Aboitiz, 2015; Fournier et al., 2015; Naumann et al., 2015). The radial organization of the modern isocortex was acquired later in crown mammals or their direct ancestors, concomitant with the differentiation of primary sensory areas. There were several embryonic mechanisms involved in the generation of a radial arrangement, including the development of an embryonic subplate, the amplification of reelin signaling, and the differentiation of a proliferative subventricular zone in the developing neuroepithelium (reviewed in Aboitiz et al., 2003; Aboitiz and Montiel, 2007; Montiel and Aboitiz, 2015; see also Abe et al., 2015). Thus, in its origins, the rudimentary isocortex

was "imprinted" by the tangential and laminar architecture of the olfactory cortex and hippocampus, and became modified into a radial design only at later stages. This view is consistent with Sanides' original notion that the cerebral cortex initially developed by the expansion of peri-allocortical regions, which serve as an interface between the neocortex and limbic cortices (Sanides, 1968).

In the common ancestor of crown mammals, the isocortex was fully developed and had a conspicuous radial organization, with four visual areas, four somatosensory areas, a gustatory or insular region, and an auditory area (Kaas, 2013). In addition, there were medial and orbitofrontal cortices rostrally and a cingulate cortex medially (Kaas, 2013). More recently, a posterior parietal and a multimodal area were also described in the opossum, suggesting that somatosensory and multimodal regions were also important in the isocortex of primitive mammals (Dooley et al., 2015). Analyzing the phylogenetic distribution of the gyrencephaly index (the degree of convolutedness) across 102 mammalian species, Lewitus et al. (2014) concluded that the common ancestor of crown mammals was most likely gyrencephalic. This implies that the small, lissencephalic brains of some species like insectivores should be viewed as derived, simplified forms, or alternatively that gyrification took place many times in modern mammals.

DISCUSSION

Brain size has increased significantly only in mammals and birds. In both cases, the increase in exploratory behavior propelled by homeothermy, benefited from increased telencephalic, associative networks conveying multimodal information about spatial relations. In mammals, early brain expansion was associated with olfactory navigation (together with somatosensory and propioceptive information), while sauropsids relayed mainly on vision. This difference established a diverging point after which mammals and birds underwent separate evolutionary trajectories, while conserving basic functional mechanisms of neural processing (Aboitiz and Montiel, 2012; Montiel and Molnár, 2013).

In the Mesozoic, early mammals were a successful clade that radiated, together with the diversification of flowering plants and the insects that coevolved with them (Aboitiz and Montiel, 2012). Nonetheless, the ecological niche that early mammals constructed was characterized by some key features like a burrowing, nocturnal way of life, and mothering behavior, together with the secretion of milk. The masticatory apparatus underwent dramatic rearrangements and liberated the ancestral jaw articulation to eventually become co-opted for impedance amplification in the middle ear ossicles. Furthermore, the loss of scales and increasing tactile behavior, particularly in the front of the mouth, together with the development of tactile vibrissae, facilitated exploratory behavior and were important in subterranean burrows.

Although we now know that Mesozoic mammals exploited a variety of ecological options, we can speculate that increasing somatosensory sensitivity in the mouth, the elaboration of direct motor cortical control of the forepaws (which is more pronounced in digging mammals; Heffner and Masterton, 1983), the development of eyelids and even possibly the loss of scales (for example the naked mole rat; Dhouailly, 2009) may be consequences of another early, burrowing "bottleneck" beside the nocturnal adaptations, that yielded profound modifications in these animals. In these conditions early mammaliaforms may have relied on predominantly olfactory information to orient themselves. The olfactory-hippocampal axis has been proposed as a key network for orienting behavior and spatial navigation (Jacobs, 2012), which, while it may be relevant in most vertebrates, was critical for the behavior of the earliest mammals. Additionally, a critical component at this point was somatosensation, particularly in the orofacial region, which projects to the dorsal pallium where the isocortex emerged. Furthermore, moderately increasing auditory sensitivity may have been relevant in subterranean life, especially for social communication. However, the major expansion of the isocortex took place in later stages, when other senses (like vision and audition) began to provide information to the hippocampus to generate multimodal, bidimensional orientation maps.

Our hypothesis has common ground with those proposed by Lynch (1986), Rowe et al. (2011), and Rowe and Shepherd (2015) in that olfactory systems were key in early mammal evolution. We add to these hypotheses the role of the emergent isocortex as a multimodal interface in the olfactory-hippocampal axis for behavioral navigation. In primitive cynodonts, orientation was based on sequential time series based on olfactory, tactile and proprioceptive cues. Expansion of the isocortex was associated with the inclusion of other sensory modalities like vision and audition, yielding bidimensional orientation maps of space rather than a linear representation of items.

Finally, we highlight the argument that brain evolution cannot be fully understood through developmental, anatomical, functional, or behavioral perspectives alone. This is because we need to combine such approaches to reach a comprehensive understanding of the genetic and epigenetic mechanisms generating developmental variability, in concert with the selective pressures exerted by the ecological and behavioral conditions animals face to successfully reproduce. Given this background, brain evolution is subject to conserved processes to which contingent adaptations are added, that may leave enduring marks in subsequent evolutionary modifications (like isocortical lamination). On the other hand, there are also conserved requirements for proper brain function and for the generation of complex perception and behavior that shape circuit and network architecture in similar ways in different lineages.

ACKNOWLEDGMENTS

Funded by the Millennium Center for the Neuroscience of Memory, Chile, Grant No. NC10-001-F to FA. We are also grateful to the reviewers of this article for their accurate observations, which significantly helped to improve this paper.

REFERENCES

Abe, P., Molnár, Z., Tzeng, Y.-S., Lai, D.-M., Arnold, S. J., and Stumm, R. (2015). Intermediate progenitors facilitate intracortical progression of thalamocortical axons and interneurons through CXCL 12 chemokine signaling. *J. Neurosci.* 35, 13053–13063. doi: 10.1523/JNEUROSCI.1488-15.2015

Aboitiz, F. (2011). Genetic and developmental homology in amniote brains. Toward conciliating radical views of brain evolution. *Brain Res. Bull.* 84, 125–136. doi: 10.1016/j.brainresbull.2010.12.003

Aboitiz, F., and Montiel, J. (2007). Origin and evolution of the vertebrate telencephalon, with special reference to the mammalian neocortex. *Adv. Anat. Embryol. Cell Biol.* 193, 1–112. doi: 10.1007/978-3-540-49761-5

Aboitiz, F., and Montiel, J. F. (2012). From tetrapods to primates: conserved developmental mechanisms in diverging ecological adaptations. *Prog. Brain Res.* 195, 3–24. doi: 10.1016/B978-0-444-53860-4.00001-5

Aboitiz, F., Morales, D., and Montiel, J. (2003). The evolutionary origin of the mammalian isocortex: towards an integrated developmental and functional approach. *Behav. Brain Sci.* 26, 535–552. discussion: 552–585. doi: 10.1017/s0140525x03000128

Aboitiz, F., and Zamorano, F. (2013). Neural progenitors, patterning and ecology in neocortical origins. *Front. Neuroanat.* 7:38. doi: 10.3389/fnana.2013.00038

Ahissar, E., and Knutsen, P. M. (2008). Object localization with whiskers. *Biol. Cybern.* 98, 449–458. doi: 10.1007/s00422-008-0214-4

Ahumada-Galleguillos, P., Fernández, M., Marin, G. J., Letelier, J. C., and Mpodozis, J. (2015). Anatomical organization of the visual dorsal ventriculr ridge in the chick (Gallus gallus): layers and columns in the avian pallium. *J. Comp. Neurol.* 523, 2618–2636. doi: 10.1002/cne.23808

Alme, C. B., Miao, C., Jezek, K., Treves, A., Moser, E. I., and Moser, M.-B. (2014). Place cells in the hippocampus: eleven maps for eleven rooms. *Proc. Natl. Acad. Sci. U.S.A.* 111, 18428–18435. doi: 10.1073/pnas.1421056111

Angielczyk, K. D., and Schmitz, L. (2014). Nocturnality in synapsids predates the origin of mammals by over 100 million years. *Proc. Biol. Sci.* 281:20141642. doi: 10.1098/rspb.2014.1642

Ashwell, K. W. S. (2012). Development of the olfactory pathways in platypus and echidna. *Brain Behav. Evol.* 79, 45–56. doi: 10.1159/000332804

Ashwell, K. W. S. (ed.). (2013). "Chemical senses: olfactory and gustatory systems," in *Neurobiology of Monotremes Brain Evolution in Our Distant Mammalian Cousins* (Collingwood, ON: CSIRO Publishing), 235–250.

Ashwell, K. W. S., Hardman, C. D., and Musser, A. M. (2014). Brain and behaviour of living and extinct echidnas. *Zoology (Jena)* 117, 349–361. doi: 10.1016/j.zool.2014.05.002

Barton, R. A., Purvis, A., and Harvey, P. H. (1995). Evolutionary radiation of visual and olfactory brain systems in primates, bats and insectivores. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 348, 381–392. doi: 10.1098/rstb.1995.0076

Bosman, C. A., and Aboitiz, F. (2015). Functional constraints in the evolution of brain circuits. *Front. Neurosci.* 9:303. doi: 10.3389/fnins.2015.00303

Brawand, D., Wahli, W., and Kaessmann, H. (2008). Loss of egg yolk genes in mammals and the origin of lactation and placentation. *PLoS Biol.* 6:e63. doi: 10.1371/journal.pbio.0060063

Brennan, P. A., and Kendrick, K. M. (2006). Mammalian social odours: attraction and individual recognition. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 361, 2061–2078. doi: 10.1098/rstb.2006.1931

Broad, K. D., Curley, J. P., and Keverne, E. B. (2006). Mother–infant bonding and the evolution of mammalian social relationships. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 361, 2199–2214. doi: 10.1098/rstb.2006.1940

Butler, A. B., Reiner, A., and Karten, H. J. (2011). Evolution of the amniote pallium and the origins of mammalian neocortex. *Ann. N.Y. Acad. Sci.* 1225, 14–27. doi: 10.1111/j.1749-6632.2011.06006.x

Buzsáki, G. (2005). Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus* 15, 827–840. doi: 10.1002/hipo.20113

Calabrese, A., and Woolley, S. M. N. (2015). Coding principles of the canonical cortical microcircuit in the avian brain. *Proc. Natl. Acad. Sci. U.S.A.* 112, 3517–3522. doi: 10.1073/pnas.1408545112

Clayton, N. S., and Emery, N. J. (2015). Avian models of human cognitive neuroscience: a proposal. *Neuron* 86, 1330–1342. doi: 10.1016/j.neuron.2015.04.024

Davachi, L., and DuBrow, S. (2015). How the hippocampus preserves order: the role of prediction and context. *Trends Cogn. Sci.* 19, 92–99. doi: 10.1016/j.tics.2014.12.004

Day, L. B., Crews, D., and Wilczynski, W. (1999). Spatial and reversal learning in congeneric lizards with different foraging strategies. *Anim. Behav.* 57, 393–407. doi: 10.1006/anbe.1998.1007

Day, L. B., Crews, D., and Wilczynski, W. (2001). Effects of medial and dorsal cortex lesions on spatial memory in lizards. *Behav. Brain Res.* 118, 27–42. doi: 10.1016/S0166-4328(00)00308-9

Dhouailly, D. (2009). A new scenario for the evolutionary origin of hair, feather, and avian scales. *J. Anat.* 214, 587–606. doi: 10.1111/j.1469-7580.2008.01041.x

Dooley, J. C., Franca, J. G., Seelke, A. M., Cooke, D. F., and Krubitzer, L. A. (2015). Evolution of mammalian sensorimotor cortex: thalamic projections to parietal cortical areas in *Monodelphis domestica*. *Front. Neuroanat.* 8:163. doi: 10.3389/fnana.2014.00163

Eichenbaum, H. (1998). Using olfaction to study memory. *Ann. N.Y. Acad. Sci.* 855, 657–669. doi: 10.1111/j.1749-6632.1998.tb10642.x

Eichenbaum, H. (2014). Time cells in the hippocampus: a new dimension for mapping memories. *Nat. Rev. Neurosci.* 15, 732–744. doi: 10.1038/nrn3827

Enjapoori, A. K., Grant, T. R., Nicol, S. C., Lefèvre, C. M., Nicholas, K. R., and Sharp, J. A. (2014). Monotreme lactation protein is highly expressed in monotreme milk and provides antimicrobial protection. *Genome Biol. Evol.* 6, 2754–2773. doi: 10.1093/gbe/evu209

Feierstein, C. E. (2012). Linking adult olfactory neurogenesis to social behavior. *Front. Neurosci.* 6:173. doi: 10.3389/fnins.2012.00173

Fournier, J., Müller, C. M., and Laurent, G. (2015). Looking for the roots of cortical sensory computation in three-layered cortices. *Curr. Biol.* 31, 119–126. doi: 10.1016/j.conb.2014.09.006

Fritzsch, B., Pan, N., Jahan, I., Duncan, J. S., Kopecky, B. J., Elliott, K. L., et al. (2013). Evolution and development of the tetrapod auditory system: an organ of Corti-centric perspective. *Evol. Dev.* 15, 63–79. doi: 10.1111/ede.12015

Fyhn, M., Molden, S., Witter, M. P., Moser, E. I., and Moser, M. B. (2004). Spatial representation in the entorhinal cortex. *Science* 305, 1258–1264. doi: 10.1126/science.1099901

Gaillard, F., Karten, H. J., and Sauvé, Y. (2013). Retinorecipient areas in the diurnal murine rodent *Arvicanthis niloticus*: a disproportionally large superior colliculus. *J. Comp. Neurol.* 521, 1699–1726. doi: 10.1002/cne.23303

Gerkema, M. P., Davies, W. I. L., Foster, R. G., Menaker, M., and Hut, R. A. (2013). The nocturnal bottleneck and the evolution of activity patterns in mammals. *Proc. Biol. Sci.* 280:20130508. doi: 10.1098/rspb.2013.0508

Gilad, Y., Wiebe, V., Przeworski, M., Lancet, D., and Pääbo, S. (2004). Loss of olfactory receptor genes coincides with the acquisition of full trichromatic vision in primates. *PLoS Biol.* 2:E5. doi: 10.1371/journal.pbio.0020005

Grant, R. A., Haidarliu, S., Kennerley, N. J., and Prescott, T. J. (2013). The evolution of active vibrissal sensing in mammals: evidence from vibrissal musculature and function in the marsupial opossum *Monodelphis domestica*. *J. Exp. Biol.* 216, 3483–3494. doi: 10.1242/jeb.087452

Grothe, B., and Pecka, M. (2014). The natural history of sound localization in mammals—a story of neuronal inhibition. *Front. Neural Circuits* 8:116. doi: 10.3389/fncir.2014.00116

Guic-Robles, E., Jenkins, W. M., and Bravo, H. (1992). Vibrissal roughness discrimination is barrelcortex-dependent. *Behav. Brain Res.* 48, 145–152. doi: 10.1016/s0166-4328(05)80150-0

Guic-Robles, E., Valdivieso, C., and Guajardo, G. (1989). Rats can learn a roughness discrimination using only their vibrissal system. *Behav. Brain Res.* 31, 285–289. doi: 10.1016/0166-4328(89)90011-9

Güntürkün, O. (2012). The convergent evolution of neural substrates for cognition. *Psychol. Res.* 76, 212–219. doi: 10.1007/s00426-011-0377-9

Haberly, L. (1990). "Comparative aspects of olfactory cortex," in *Cerebral Cortex,* Vol. 8B, eds E. G. Jones and A. Peters (New York, NY: Springer), 137–164.

Hafting, T., Fyhn, M., Molden, S., Moser, M. B., and Moser, E. I. (2005). Microstructure of a spatial map in the entorhinal cortex. *Nature* 436, 801–806. doi: 10.1038/nature03721

Hall, M. I., Kamilar, J. M., and Kirk, E. C. (2012). Eye shape and the nocturnal bottleneck of mammals. *Proc. Biol. Sci.* 279, 4962–4968. doi: 10.1098/rspb.2012.2258

Hampson, R. E., Simeral, J. D., and Deadwyler, S. A. (1999). Distribution of spatial and nonspatial information in dorsal hippocampus. *Nature* 402, 610–614. doi: 10.1038/45154

Hartmann, M. J., and Bower, J. M. (2001). Tactile responses in the granule cell layer of cerebellar folium crus IIa of freely behaving rats. *J. Neurosci*. 21, 3549–3563. doi: 10.1016/0166-4328(87)90243-9

Heesy, C. P., and Hall, M. I. (2010). The nocturnal bottleneck and the evolution of mammalian vision. *Brain Behav. Evol.* 75, 195–203. doi: 10.1159/000314278

Heffner, R. S., and Heffner, H. E. (1992a). "Evolution of sound localization in mammals," in *The Evolutionary Biology of Hearing*, eds D. B. Webster, A. N. Popper, and R. R. Fay (New York, NY: Springer-Verlag), 691–715.

Heffner, R. S., and Heffner, H. E. (1992b). Visual Factors in sound localization in mammals. *J. Comp. Neurol.* 317, 219–232. doi: 10.1002/cne.903170302

Heffner, R. S., and Masterton, R. B. (1983). The role of the corticospinal tract in the evolution of human digital dexterity. *Brain Behav. Evol.* 23, 165–183. doi: 10.1159/000121494

Hoover, K. C. (2010). Smell with inspiration: the evolutionary significance of olfaction. *Am. J. Phys. Anthropol.* 143(Suppl. 51), 63–74. doi: 10.1002/ajpa.21441

Jacobs, L. F. (2012). From chemotaxis to the cognitive map: the function of olfaction. *Proc. Natl. Acad. Sci. U.S.A.* 109(Suppl. 1), 10693–10700. doi: 10.1073/pnas.1201880109

Kaas, J. H. (2013). The evolution of brains from early mammals to humans. *Wiley Interdiscip. Rev. Cogn. Sci.* 4, 33–45. doi: 10.1002/wcs.1206

Kelly, J. B. (1980). Effects of auditory cortical-lesions on sound localization by the rat. *J. Neurophys.* 44, 1161–1174.

Kelly, J. B., and Kavanagh, G. L. (1986). Effects of auditory cortical lesions on pure-tone sound localization by the albino rat. *Behav. Neurosci.* 100, 569–575. doi: 10.1037/0735-7044.100.4.569

Kielan-Jaworowska, Z., Cifelli, R., and Luo, Z.-X. (2004). *Mammals from the Age of Dinosaurs*. New York, NY: Columbia University Press.

Knutsen, P. M., Biess, A., and Ahissar, E. (2008). Vibrissal kinematics in 3D: tight coupling of azimuth, elevation, and torsion across different whisking modes. *Neuron* 59, 35–42. doi: 10.1016/j.neuron.2008.05.013

Krupa, D. J., Matell, M. S., Brisben, A. J., Oliveira, L. M., and Nicolelis, M. (2001). Behavioral properties of the trigeminal somatosensory system in rats performing whisker-dependent tactile discriminations. *J. Neurosci.* 21, 5752–5763. doi: 10.1002/cne.902630209

Krupic, J., Bauza, M., Burton, S., Barry, C., and O'Keefe, J. (2015). Grid cell symmetry is shaped by environmental geometry. *Nature* 518, 232–235. doi: 10.1038/nature14153

Lee, C. C., and Middlebrooks, J. C. (2011). Auditory cortex spatial sensitivity sharpens during task performance. *Nat. Neurosci.* 14, 108–114. doi: 10.1038/nn.2713

Leng, G., Caquineau, C., and Sabatier, N. (2005). Regulation of oxytocin secretion. *Vitam. Horm.* 71, 27–58. doi: 10.1016/S0083-6729(05)71002-5

Lenschow, C., and Brecht, M. (2015). Barrel cortex membrane potential dynamics in social touch. *Neuron* 85, 718–725. doi: 10.1016/j.neuron.2014.12.059

Lévy, F., Keller, M., and Poindron, P. (2004). Olfactory regulation of maternal behavior in mammals. *Horm. Behav.* 46, 284–302. doi: 10.1016/j.yhbeh.2004.02.005

Lewitus, E., Kelava, I., Kalinka, A. T., Tomancak, P., and Huttner, W. B. (2014). An adaptive threshold in mammalian neocortical evolution. *PLoS Biol.* 12:e1002000. doi: 10.1371/journal.pbio.1002000

Lisman, J. E. (2007). Role of the dual entorhinal inputs to hippocampus: a hypothesis based on cue/action (non-self/self) couplets. *Prog. Brain Res.* 163, 615–625. doi: 10.1016/S0079-6123(07)63033-7

Liu, Z., Li, G.-H., Huang, J.-F., Murphy, R. W., and Shi, P. (2012). Hearing aid for vertebrates via multiple episodic adaptive events on prestin genes. *Mol. Biol. Evol.* 29, 2187–2198. doi: 10.1093/molbev/mss087

Luo, Z.-X. (2007). Transformation and diversification in early mammal evolution. *Nature* 450, 1011–1019. doi: 10.1038/nature06277

Luo, Z. X., Crompton, A. W., and Sun, A. L. (2001). A new mammaliaform from the early Jurassic and evolution of mammalian characteristics. *Science* 292, 1535–1540. doi: 10.1126/science.1058476

Luo, Z.-X., Ruf, I., Schultz, J. A., and Martin, T. (2011). Fossil evidence on evolution of inner ear cochlea in Jurassic mammals. *Proc. Biol. Sci.* 278, 28–34. doi: 10.1098/rspb.2010.1148

Lynch, G. (1986). *Synapses, Circuits, and The Beginnings of Memory*. Cambridge, MA: MIT Press.

MacDonald, C. J., Lepage, K. Q., Eden, U. T., and Eichenbaum, H. (2011). Hippocampal "time cells" bridge the gap in memory for discontiguous events. *Neuron* 71, 737–749. doi: 10.1016/j.neuron.2011.07.012

Manley, G. A. (2012). Evolutionary paths to mammalian cochleae. *J. Assoc. Res. Otolaryngol.* 13, 733–743. doi: 10.1007/s10162-012-0349-9

Manley, G. A. (2013). Mosaic evolution of the mammalian auditory periphery. *Adv. Exp. Med. Biol.* 787, 3–9. doi: 10.1007/978-1-4614-1590-9_1

Montiel, J. F., and Aboitiz, F. (2015). Pallial patterning and the origin of the isocortex. *Front. Neurosci.* 9:377. doi: 10.3389/fnins.2015.00377

Montiel, J. F., and Molnár, Z. (2013). The impact of gene expression analysis on evolving views on avian brain organization. *J. Comp. Neurol.* 521, 3604–3613. doi: 10.1002/cne.23403

Naumann, R. K., Ondracek, J. M., Reiter, S., Shein-Idelson, M., Tosches, M. A., Yamawaki, T. M., et al. (2015). The reptilian brain. *Curr. Biol.* 25, R301–R321. doi: 10.1016/j.cub.2015.02.049

Nieuwenhuys, R. (1994). The neocortex - an overview of its evolutionary development, structural organization and synaptology. *Anat. Embryol.* 190, 307–337.

Niimura, Y. (2009). On the origin and evolution of vertebrate olfactory receptor genes: comparative genome analysis among 23 chordate species. *Genome Biol. Evol.* 1, 34–44. doi: 10.1093/gbe/evp003

Porter, R. H. (2004). The biological significance of skin-to-skin contact and maternal odours. *Acta Paediatr.* 93, 1560–1562. doi: 10.1111/j.1651-2227.2004.tb00843.x

Poucet, B., Sargolini, F., Song, E. Y., Hangya, B., Fox, S., and Muller, R. U. (2013). Independence of landmark and self-motion-guided navigation: a different role for grid cells. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 369:20130370. doi: 10.1098/rstb.2013.0370

Powers, A. S. (1990). "Brain mechanisms of learning in reptiles," in *Neurobiology of Comparative Cognition*, eds R. P. Kesner and D. S. Olton (New York, NY: Erlbaum Press), 75–87.

Preston, A. R., and Eichenbaum, H. (2013). Interplay of hippocampus and prefrontal cortex in memory. *Curr. Biol.* 23, R764–R773. doi: 10.1016/j.cub.2013.05.041

Raihani, G., González, D., Arteaga, L., and Hudson, R. (2009). Olfactory guidance of nipple attachment and suckling in kittens of the domestic cat: inborn and learned responses. *Dev. Psychobiol.* 51, 662–671. doi: 10.1002/dev.20401

Reep, R. L., Finlay, B. L., and Darlington, R. B. (2007). The limbic system in Mammalian brain evolution. *Brain Behav. Evol.* 70, 57–70. doi: 10.1159/000101491

Rodríguez, F., López, J. C., Vargas, J. P., Broglio, C., Gómez, Y., and Salas, C. (2002). Spatial memory and hippocampal pallium through vertebrate evolution: insights from reptiles and teleost fish. *Brain Res. Bull.* 57, 499–503. doi: 10.1016/S0361-9230(01)00682-7

Rowe, T. (1996a). Brain heterochrony and origin of the mammalian middle ear. *Mem. Cal. Acad. Sci.* 20, 71–95.

Rowe, T. (1996b). Coevolution of the mammalian middle ear and neocortex. *Science* 273, 651–654. doi: 10.1126/science.273.5275.651

Rowe, T. B., Macrini, T. E., and Luo, Z. X. (2011). Fossil evidence on origin of the mammalian brain. *Science* 332, 955–957. doi: 10.1126/science.1203117

Rowe, T. B., and Shepherd, G. M. (2015). The role of ortho-retronasal olfaction in mammalian cortical evolution. *J. Comp. Neurol.* doi: 10.1002/cne.23802. [Epub ahead of print].

Ruf, I., Maier, W., Rodrigues, P. G., and Schultz, C. L. (2014). Nasal anatomy of the non-mammaliaform cynodont *Brasilitherium riograndensis* (Eucynodontia, Therapsida) reveals new insight into mammalian evolution. *Anat. Rec. (Hoboken)* 297, 2018–2030. doi: 10.1002/ar.23022

Sahay, A., Wilson, D. A., and Hen, R. (2011). Pattern separation: a common function for new neurons in hippocampus and olfactory bulb. *Neuron* 70, 582–588. doi: 10.1016/j.neuron.2011.05.012

Sanai, N., Nguyen, T., Ihrie, R. A., Mirzadeh, Z., Tsai, H.-H., Wong, M., et al. (2011). Corridors of migrating neurons in the human brain and their decline during infancy. *Nature* 478, 382–386. doi: 10.1038/nature10487

Sanchez-Andrade, G., and Kendrick, K. M. (2009). The main olfactory system and social learning in mammals. *Behav. Brain Res.* 200, 323–335. doi: 10.1016/j.bbr.2008.12.021

Sanides, F. (1968). The architecture of the cortical taste nerve areas in squirrel monkey (*Saimiri sciureus*) and their relationships to insular, sensorimotor and prefrontal regions. *Brain Res.* 8, 97–124. doi: 10.1016/0006-8993(68)90174-1

Schaal, B. (2010). Mammary odor cues and pheromones: mammalian infant-directed communication about maternal state, mammae, and milk. *Vitam. Horm.* 83, 83–136. doi: 10.1016/S0083-6729(10)83004-3

Schaal, B., Coureaud, G., Doucet, S., Delaunay-El Allam, M., Moncomble, A.-S., Montigny, D., et al. (2009). Mammary olfactory signalisation in females and odor processing in neonates: ways evolved by rabbits and humans. *Behav. Brain Res.* 200, 346–358. doi: 10.1016/j.bbr.2009.02.008

Schaal, B., Coureaud, G., Langlois, D., Giniès, C., and Sémon, E. (2003). Chemical and behavioural characterization of the rabbit mammary pheromone. *Nature* 24, 68–72. doi: 10.1038/nature01739

Shepherd, G. M. (2007). Perspectives on olfactory processing, conscious perception, and orbitofrontal cortex. *Ann. N.Y. Acad. Sci.* 1121, 87–101. doi: 10.1196/annals.1401.032

Shepherd, G. M. (2011). The microcircuit concept applied to cortical evolution: from three-layer to six-layer cortex. *Front. Neuroanat.* 5:30. doi: 10.3389/fnana.2011.00030

Smart, I. H. M. (2008). Evolution, development, and initial function of the mammalian neocortex: response of the germinal zones to endothermy. *Anat. Rec. (Hoboken)* 291, 28–48. doi: 10.1002/ar.20629

Solovei, I., Kreysing, M., Lanctôt, C., Kösem, S., Peichl, L., Cremer, T., et al. (2009). Nuclear architecture of rod photoreceptor cells adapts to vision in mammalian evolution. *Cell* 137, 356–368. doi: 10.1016/j.cell.2009.01.052

Song, J., Christian, K. M., and Ming, G. (2012). Modification of hippocampal circuitry by adult neurogenesis. *Dev. Neurobiol.* 72, 1032–1043. doi: 10.1002/dneu.22014

Stevenson, R. J. (2009). Phenomenal and access consciousness in olfaction. *Conscious. Cogn.* 18, 1004–1017. doi: 10.1016/j.concog.2009.09.005

Striedter, G. F. (2015). Evolution of the hippocampus in reptiles and birds. *J. Comp. Neurol.* doi: 10.1002/cne.23803. [Epub ahead of print].

Taube, J. S. (2007). The head direction signal: origins and sensory-motor integration. *Annu. Rev. Neurosci.* 30, 181–207. doi: 10.1146/annurev.neuro.29.051605.112854

Vanderwolf, C. H. (2001). The hippocampus as an olfacto-motor mechanism: were the classical anatomists right after all? *Behav. Brain Res.* 127, 25–47. doi: 10.1016/s0166-4328(01)00354-0

Vega-Zuniga, T., Medina, F. S., Fredes, F., Zuniga, C., Severín, D., Palacios, A. G., et al. (2013). Does nocturnality drive binocular vision? Octodontine rodents as a case study. *PLoS ONE* 8:e84199. doi: 10.1371/journal.pone.0084199

Wacker, D. W., and Ludwig, M. (2012). Vasopressin, oxytocin, and social odor recognition. *Horm. Behav.* 61, 259–265. doi: 10.1016/j.yhbeh.2011.08.014

Walls, G. L. (1942). *The Vertebrate Eye and its Adaptive Radiation*. Cranbrook, BC: Bloomfield Hills, Mich; Cranbrook Institute of Science.

Wang, Y., Brzozowska-Prechtl, A., and Karten, H. J. (2010). Laminar and columnar auditory cortex in avian brain. *Proc. Natl. Acad. Sci. U.S.A.* 107, 12676–12681. doi: 10.1073/pnas.1006645107

Wang, Y., Hu, Y., Meng, J., and Li, C. (2001). An ossified Meckel's cartilage in two Cretaceous mammals and origin of the mammalian middle ear. *Science* 294, 357–361. doi: 10.1126/science.1063830

Warren, W. C., Hillier, L. W., Marshall Graves, J. A., Birney, E., Ponting, C. P., Grützner, F., et al. (2008). Genome analysis of the platypus reveals unique signatures of evolution. *Nature* 453, 175–183. doi: 10.1038/nature06936

Yopak, K. E., Lisney, T. J., Darlington, R. B., Collin, S. P., Montgomery, J. C., and Finlay, B. L. (2010). A conserved pattern of brain scaling from sharks to primates. *Proc. Natl. Acad. Sci. U.S.A.* 107, 12946–12951. doi: 10.1073/pnas.1002195107

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

REVIEW
published: 27 March 2018
doi: 10.3389/fnins.2018.00174

A Brain for Speech. Evolutionary Continuity in Primate and Human Auditory-Vocal Processing

*Francisco Aboitiz**

Centro Interdisciplinario de Neurociencias, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

In this review article, I propose a continuous evolution from the auditory-vocal apparatus and its mechanisms of neural control in non-human primates, to the peripheral organs and the neural control of human speech. Although there is an overall conservatism both in peripheral systems and in central neural circuits, a few changes were critical for the expansion of vocal plasticity and the elaboration of proto-speech in early humans. Two of the most relevant changes were the acquisition of direct cortical control of the vocal fold musculature and the consolidation of an auditory-vocal articulatory circuit, encompassing auditory areas in the temporoparietal junction and prefrontal and motor areas in the frontal cortex. This articulatory loop, also referred to as the phonological loop, enhanced vocal working memory capacity, enabling early humans to learn increasingly complex utterances. The auditory-vocal circuit became progressively coupled to multimodal systems conveying information about objects and events, which gradually led to the acquisition of modern speech. Gestural communication accompanies the development of vocal communication since very early in human evolution, and although both systems co-evolved tightly in the beginning, at some point speech became the main channel of communication.

Keywords: speech, working memory, evolution, animal vocalization, arcuate fasciculus

OPEN ACCESS

Edited by:
Ralph L. Holloway,
Columbia University, United States

Reviewed by:
David Geary,
University of Missouri, United States
James Rilling,
Independent Researcher, Atlanta, GA, United States

***Correspondence:**
Francisco Aboitiz
faboitiz@puc.cl

Specialty section:
This article was submitted to Social and Evolutionary Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *13 October 2017*
Accepted: *05 March 2018*
Published: *27 March 2018*

Citation:
Aboitiz F (2018) A Brain for Speech. Evolutionary Continuity in Primate and Human Auditory-Vocal Processing. Front. Neurosci. 12:174. doi: 10.3389/fnins.2018.00174

INTRODUCTION

Homo sapiens is an outstanding and successful species, arguably due to our capacity for speech and language. In previous works, my colleagues and I have emphasized that the emergence of the phonological loop, an auditory-vocal circuit involved in verbal working memory, was a radical innovation in speech origins, as it expanded auditory-vocal short term memory capacity, enabling early humans to learn increasingly complex vocal utterances (Aboitiz, 1995, 2012, 2017; Aboitiz and García, 1997; Aboitiz et al., 2006a,b, 2010). In this article, I will review and extend these ideas, some but not all of which have been put forward recently (Aboitiz, 2017). Basically, the main contribution of this paper is to provide a comprehensive but summarized scenario, starting from the preconditions existent in non-human primates and the subsequent development of a sophisticated neural control of vocalizations in early humans.

PRECONDITIONS TO SPEECH: PRIMATE ADAPTATIONS

Humans belong to the order Primates, which originated in the late Cretaceous, some 65 million years ago. Primates are characterized by arboreal habits, superior grasping abilities and good frontal

vision, initially associated with nocturnal habits. More derived primates are diurnal animals, and display a complex visual system with color vision, which is useful for fruit recognition (Fleagle, 2013).

Primate Brains

Another feature of primates is their brain size, that has been related by many to higher cognitive capacity. Not only primates have a brain that doubles the size of other mammals of the same body size, but also they display a much higher neuronal density than that of other mammals in their cerebral cortices (Herculano-Houzel et al., 2015). Humans have the largest brain and the highest number of neurons of all primates (Herculano-Houzel et al., 2015). This increase in brain size and neuron number has gradually developed along the *Homo* lineage, partly associated with increase in body size but growing disproportionately to the latter, making our brains the largest in size (and with more neurons) in relation to body size of all animals (Aboitiz, 2017). A contentious issue is whether the prefrontal cortex has grown disproportionately in primates, especially in humans. Altogether, the recent evidence suggests that in humans and primates, the prefrontal cortex grows concomitantly with other higher order areas in the parietal and temporal regions, while lower order sensorimotor areas evolve more conservatively (see next section) (Margulies et al., 2016).

Paleoanthropological Evidence of Human Brain Evolution

The study of fossil endocasts of hominin brains has provided important information about the size and shape of the brains, which increased in size from some 500 cc. in australopithecines to more than 1,000 cc. in late *Homo erectus*. More modern *Homo* species like Neanderthals, Denisovans, and modern humans show a further increase in brain size up to about 1,500 cc. A contentious issue has been the identification of Broca's language region in early hominin endocasts. Australopithecines lack a human-like Broca's cap region, but specimen KNM-ER 1470 (*H. Rudolfiensis*) displays a more advanced morphology in this area (Holloway, 2017). Compared to other human fossils, Neanderthals and modern humans display an increased depth of the anterior fossa that corresponds to part of Broca's region and relatively wider frontal lobes (Bruner and Holloway, 2010). These are also the only human species with the frontal lobes located entirely over the orbits (Bruner et al., 2014), but the functional implications of these findings are unclear (Balzeau et al., 2014; Bruner, 2017). On the other hand, both humans and apes display larger frontal lobes on the right hemisphere and a larger occipital lobe on the left hemisphere, although asymmetries are more marked in fossil hominins (Bruner, 2017; Holloway, 2017).

The parietal surface of the endocranium has evidenced more clear differences among early humans. Firstly, the lunate sulcus that separates parietal cortex from the primary visual cortex in apes, is absent or very fragmented in modern humans, presumably via expansion of the parietal lobe (Holloway, 2017). Neanderthals and modern humans exhibit wider upper parietal regions than other hominids, and modern humans have these regions larger than Neanderthals (Bruner et al., 2011). The two regions showing most cranial differences are the midsagittal precuneus and the intraparietal sulcus, although both are highly variable even among modern humans (Pereira-Pedro et al., 2017). The precuneus and the intraparietal lobe are important nodes for large scale neural networks including the default mode network and circuits for hand and eye coordination (Bruner, 2017). This evidence fits the increasingly globular shape of the modern human cranium (Neubauer et al., 2018). The expansion of these regions may also relate to increasing hand control and tool making (Stout and Hecht, 2017), and to other functions like orientation, attention, self-awareness, and some aspects of language (see below).

Hand Control and Gestures

Primate hands (and feet) are more prehensile than those of other mammals, featuring an opposable thumb suitable for grasping branches and leaves or fruit, that can be brought to the mouth for consumption. Furthermore, their fingers have nails instead of claws, and highly sensitive finger buds below the nails. These morphological features are related to a direct, monosynaptic corticospinal innervation of the cervical spinal cord motoneurons controlling the hand muscles, a character associated with hand dexterity and found only in primates (Fleagle, 2013). Nonetheless, other mammals like rodents have a transient, direct corticospinal projection to hand motoneurons, that is present postnatally but is eliminated during development, a process mediated by the gene PlexA1 (Gu et al., 2017). Importantly, PlexA1 mutant mice maintain the direct corticospinal projection in adulthood, and display enhanced manual dexterity than normal animals. In addition, grasping behavior development requires a neonatal transient visual pathway in primates (Mundinano et al., 2018).

Grasping behavior also depends on complex neural networks involving parietal and premotor areas as critical nodes in a widespread network that includes temporoparietal and prefrontal areas. In this circuit, visual information about both the nature and position of the object to be grasped are used for coordinating a precise motor sequence that includes reaching the object and then grasping it (Borra et al., 2017). A great deal of excitement was produced by the discovery of grasping mirror neurons in area F5 of the ventral premotor cortex of the monkey, which fire both when the monkey executes a grasping action and when it observes another individual performing the action (di Pellegrino et al., 1992). These neurons were soon interpreted as involving a motoric representation on the other's behavior, and were considered as essential to understand the goals and intentions of others by activating one's own motor programs emulating the behavior (Rizzolatti et al., 1996). Afterwards, Rizzolatti and Arbib (1998; Arbib, 2012) put forward the hypothesis that

Abbreviations: A, primary auditory area; AC, anterior cingulate cortex; AF, arcuate fasciculus; AM, amygdala; DLF, dorsolateral frontal cortex; EC, extreme capsule; ILF, inferior, longitudinal fasciculus; LC, laryngeal and orofacial cortex; MLF, middle longitudinal fasciculus; MTG, middle temporal gyrus; NA, nucleus ambiguous; PAG, periaqueductal gray; SLF, superior longitudinal fasciculus (ventral); STG, superior temporal gyrus; STS, superior temporal sulcus; UF, uncinate fasciculus; V1, primary visual area.

grasping mirror neurons were essential for the origin of language, and revived the theory that the earliest forms of symbolic communication were gestural instead of vocal.

The notion of mirror neurons as representing other agent's intentions or goals has been questioned by some authors and this is now a matter of intense debate (Cook et al., 2014; Hickok, 2014). Concerning the gestural theory of language origins, the core proposal of the present paper is how speech itself was acquired, regardless on whether the first symbols were hand- or mouth- based. Nonetheless, although not an implausible hypothesis, the gestural theory is highly speculative and contestable (Bosman et al., 2005; Aboitiz, 2013). One of its central assumptions is that because monkeys and apes have voluntary control of hands but not of voice, language must have started from manual gestures and was only later transmitted to the vocal system by some unknown mechanism (the theory says very little about speech origins). However, voluntary hand control is widespread among primates and language is uniquely human. Thus, something else than hand control is needed to account for human language. Moreover, monkeys and apes have voluntary control of the lips, which are essential for speech, and orangutans have been shown to imitate human speech (Lameira et al., 2014). In this line, some adherents to the mirror neuron hypothesis propose a role of lip movements and hand-mouth interactions in early human communication (Coudé and Ferrari, in press), but this is disputed by some other mirror neuron theorists (Arbib, 2012). More generally, the conjecture that hand signing made possible the development of vocal plasticity leading to speech contrasts with abundant comparative evidence that voluntary control of vocalizations and vocal learning can evolve without necessity of a hand-grasping circuitry, as it occurs in songbirds, bats and marine mammals (Aboitiz, 2012, 2017). Perhaps more parsimonious is the notion that the human voice developed in parallel and coevolved with hand control.

Tool Making Behavior

Tool making behavior is observed in monkeys and apes, but fossil hominids excelled by far the other primate species. In modern humans, stone tool making relies on a network encompassing visual areas, the inferior parietal lobe and ventral premotor areas. Furthermore, the ventral aspect of the superior longitudinal fasciculus (SLF) connects inferior parietal and premotor areas, and is larger and more asymmetric (with the right side larger) in humans than apes (Budisavljevic et al., 2015; Putt et al., 2017; Stout and Hecht, 2017). As these networks may show some overlap with the speech networks to be described below, it is tempting to hypothesize that speech and tool making reinforced each other in human evolution. However, the relation between tool-making behavior and speech is unlikely to be direct, as there is conflicting evidence as to whether spoken instructions improve tool-making learning in modern humans (Putt et al., 2014; Morgan et al., 2015; Cataldo et al., 2018). On the other hand, speech acquisition in children obviously does not depend on tool making behavior. While gesturing and especially imitation were probably more relevant for tool-making behavior in our ancestors, learned vocalizations may have developed as a parallel acquisition associated with social rather than technological demands, in an increasingly complex protoculture where both gestures and vocalizations were essential components of communication (Cataldo et al., 2018). Finally, tool-making requires a clear division of labor between both hands, which may have contributed to the generation of language asymmetries in humans (Uomini and Meyer, 2013; Hecht et al., 2015), although communication constraints may have also been important (see below).

Vocal and Orofacial Behavior in Non-human Primates

Basal primates like lemurs show a strepshirhine condition shared with other mammals, where the lips elevate to the nose. On the other hand, some prosimians like the tarsius and the rest of the primates display a haplorhine condition in which the upper lip becomes separated from the nose by a band of skin, making a continuous lip around the mouth that is used for feeding and communication (Fleagle, 2013). In fact, lips are highly movable in higher primates, and they display a series of social signals using lip movements. Lip-smacking is a common affiliative behavior used by many primates, but there are other types of voiceless calls, like "clicks," "kisses," and "whistles," that are produced by the upper vocal tract, particularly the lips. In fact, non-human primates have a sophisticated, very likely voluntary, neural control of their lips, of which we know little about yet (Lameira et al., 2014; Coudé and Ferrari, in press). Recent reports have described interesting similarities between monkey lipsmacking and human lip movements while speaking, which follow similar developmental trends (Ghazanfar et al., 2012; Morrill et al., 2012). A second organ involved in human speech is the tongue, but more research is needed on how non-human primates use it for feeding or communicating.

Non-human primates are highly vocal animals, that communicate intensely through coordinated calls generated by movements of the laryngeal vocal folds (Belyk and Brown, 2017). Non-human primate vocalizations are usually fixed in structure and species-specific, but can be modulated according to social context, and there is voluntary control of when and what to vocalize (Hage et al., 2013; Hage and Nieder, 2016). Like humans, apes are able to modulate the fundamental frequency of their vocalizations, depending on the listener and social context (Pisanski et al., 2016). Furthermore, in some primates like marmosets, vocalizations develop in infants form a variable structure that gradually consolidates in clustered acoustical signals during maturation, just like in infants and songbirds, a process driven by maternal feedback (Takahashi et al., 2015; Hage et al., 2016). In addition, some primates like gibbons and marmosets engage in reciprocal "conversations" that can last for a long time (Geissmann, 2002; Takahashi et al., 2013). While the gibbon's duets are rather stereotyped in structure, marmosets appear to have some variability in their vocalizations (Thinh et al., 2011; Koda et al., 2013; Hage et al., 2016; Takahashi et al., 2016; Pomberger et al., 2018).

Lieberman (1968) observed that the larynx is in a lower position in the vocal tract in humans than in other primates, which was attributed to the development of a resonance cavity

in the upper vocal tract for the production of vowels. More recent studies have found that this character is also present in other animals like male deer, a result of sexual selection for generating lower frequencies and give the impression of a larged body size (Fitch and Reby, 2001). Yet, early humans may have taken advantage of this condition to optimize vowel production. As will be discussed below, only humans among primates have direct cortical control over laryngeal musculature, which may have evolved together with the descent of the larynx in our ancestors.

Nonetheless, a recent study showed that all movements used by humans when speaking can be executed by monkeys, and computer simulations of monkey vocalizations were able to generate human-like speech (Fitch et al., 2016; but see Fitch et al., 2017; Lieberman, 2017). Another study showed that monkeys naturally emit sounds similar to human vowels, but they do not organize them into complex phonological sequences, presumably because they lack direct cortical control of these muscles (Boë et al., 2017). Another aspect of interest is the coordination of lips and larynx during communication. While in most primates, upper vocal tract movements (lips) dissociate from vocalizations (emitted by the lower vocal tract, i.e., the larynx), in human speech these become tightly coordinated. An intermediate situation is found in the "wobble" call of the gelada, in which vocalizations are synchronized with lip smacking (Ghazanfar and Takahashi, 2014a,b). Other interesting findings are the reports of human voice imitation in orangutans, who in addition have incredibly movable lips (Lameira et al., 2016).

Descending Control of Face and Throat

Vocalizations and orofacial movements are controlled by several brainstem nuclei, such as the trigeminal motor nucleus innervating jaw musculature, the hypoglossal nucleus driving tongue movements, the facial nucleus controlling face and lip movements, and finally the ambiguus nucleus innervating the vocal folds in the larynx. In addition, vocalizations depend on a tight control of respiratory muscles. These nuclei relate to brainstem central pattern generators that produce cyclic activity for behaviors like chewing, swallowing, drinking, laughing and swallowing (Jürgens, 2009; Hage and Nieder, 2016). It is most likely that these circuits were recruited and remodeled for the development of human speech, as for example, respiratory movements have to be much more controlled during speech than during primate vocalizations (Ghazanfar and Rendall, 2008; Ghazanfar and Takahashi, 2014a; Belyk and Brown, 2017).

In turn, these brainstem circuits are controlled by an upper level network that involves the cingulate cortex, the orbitofrontal cortex, the insula, and the amygdala, which connect to the mesencephalic periaqueductal gray and then reach the pacemaker circuits in the brainstem reticular formation (**Figure 1**; Simonyan and Jürgens, 2003; Jürgens, 2009; Hage and Nieder, 2016; Holstege and Subramanian, 2016; Coudé and Ferrari, in press). This circuit is considered to be responsible for triggering reflex, non-volitional vocalizations, and is also involved in the rewarding and emotional dimension of communication. In addition to this circuit, but well connected to it, there is a second circuit centered in the motor and premotor orofacial and laryngeal cortices, that is connected with the basal ganglia, thalamus and cerebellum, and is involved in volitional control of vocalizations. While in non-human primates, the laryngeal motor representation is located in the ventral premotor cortex, in humans it is located in the motor cortex, adjacent to the orofacial motor representation (Belyk and Brown, 2017). The human laryngeal motor cortex also participates in respiratory control, and is proposed to be duplicated, with ventral and dorsal components (Belyk and Brown, 2017).

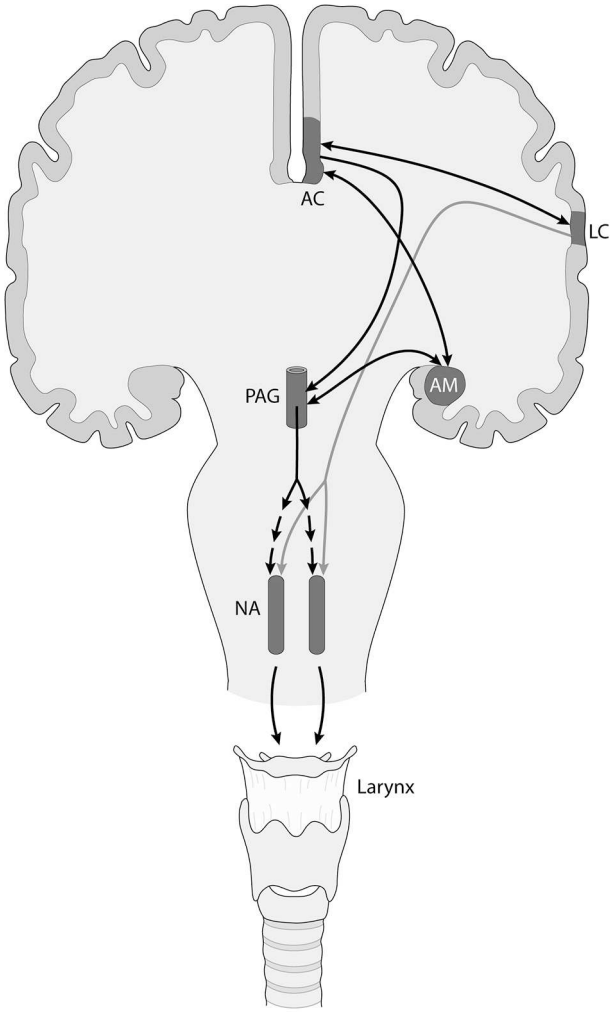


FIGURE 1 | Simplified scheme of the descending neuronal control of the nucleus ambiguus (NA), that controls vocal fold musculature, in primates including humans. There are two different neural networks involved, an emotionally controlled, non-volitional one (black arrows) that includes limbic and other components like the anterior cingulate (AC) cortex and the amygdalar complex (AM), which project to the mesencephalic periaqueductal gray (PAG). In turn, the PAG sends a polisynaptic projection to the neurons of the NA (segmented arrows). In addition, there is a descending projection from the laryngeal motor cortex (LC) to the NA (gray arrow), that exerts voluntary control over vocalizations. These two pathways are connected via the frontal aslant tract (arrow connecting AC with LC). A similar organization is found in the networks controlling the brainstem nuclei innervating the musculature of the upper vocal tract (lips and tongue), which for simplicity are not shown.

As mentioned, the non-volitional and the volitional vocalization circuits are interconnected, but their connectivity has been claimed to increase in the human lineage. In this context, the frontal aslant tract connects dorsomedial frontal cortex with ventrolateral frontal and prefrontal cortex, and its maturation has been related to speech acquisition in infants (Catani et al., 2013), which makes it a prime candidate to bridge both circuits (**Figure 1**). Furthermore, the laryngeal and probably the orofacial motor cortex have connections with somatosensory, inferior parietal and posterior superior temporal (auditory) areas, possibly participating in an audio-vocal circuit that transforms auditory input in vocal output signals and vice versa (**Figure 2**; Kumar et al., 2016; Hickok, 2017).

The orofacial and laryngeal motor cortices send descending projections to the reticular formation, controlling the distinct cranial motor nuclei. It has been proposed that, as opposed to the rest of primates, in humans the laryngeal cortex sends a direct projection to the nucleus ambiguus controlling the vocal folds (**Figure 1**), while in other primates these axons reach nearby interneurons that themselves project to the nucleus ambiguus (Jürgens, 2009). A direct projection to the nucleus retroambiguus, controlling respiratory movements has also been proposed (Belyk and Brown, 2017). These characters have been considered to be key for the acquisition of vocal learning capacity in humans. A striking parallelism has been found in songbirds, where there is a direct descending projection from a telencephalic motor nucleus to the cranial nucleus controlling syrinx musculature. Vocal non-learning birds, like non-human primates, lack this direct projection (Petkov and Jarvis, 2012).

Premotor and Prefrontal Control of Vocal and Orofacial Behavior

In non-human primates, there is also prefrontal control of the orofacial and laryngeal musculature. Petrides and collaborators reported that stimulation of area 44 in the ventrolateral prefrontal cortex of monkeys (homologous to posterior Broca's area in the human) triggers orofacial movements and very rarely hand movements (Petrides et al., 2005). Coudé et al. (2011) found neurons firing with voluntary vocalizations in the macaque ventral premotor cortex, and Hage and Nieder (2013) reported similar properties in the monkey prefrontal cortex, specifically in area 44 and surrounding regions. Furthermore, neuronal activity in the prefrontal cortex of marmosets has been found to correlate, and even predict, whether an animal will engage or not in a reciprocal, "conversational" loop with another individual (Nummela et al., 2017).

Additional studies have reported neurons with mirror properties for mouth movements in the ventral premotor cortex of the monkey, that activate both during food ingestion and during communication behaviors like lip-smacking (Ferrari et al., 2003, 2017). Like grasping mirror neurons, mouth mirror neurons fire both during the execution and the observation of mouth movements. Interestingly, the mouth representation overlaps with the hand representation in the ventral premotor cortex, where neurons involved in hand, mouth and gestural behavior are intermingled (Coudé and Ferrari, in press). This overlap may be important for hand-mouth coordination behavior, a character that is probably ancestral to mammals but acquires more relevance in primates, both for feeding and communicative purposes (Coudé and Ferrari, in press). Like the laryngeal motor cortex, the representation of face and lips is connected with the non-volitional/emotional vocalization circuit described above, including the anterior cingulate cortex, orbitofrontal cortex, insula, amygdala and other regions (Hage and Nieder, 2016; Ferrari et al., 2017). Acoustical, instead of visual, mirror neuron activity has been also found with sounds that are associated with actions like tearing a paper (Kohler et al., 2002), but to date no visual or acoustical mirror activity has been reported for monkey vocalizations (but see below; Hage and Nieder, 2015).

Auditory Networks in the Monkey

The primate auditory cortex is organized in three concentrical rings located in the superior temporal lobe, in which there is a core region containing primary and secondary auditory areas, a belt region surrounding it, that houses higher order auditory regions, and a parabelt area that projects to surrounding cortices of the temporal, parietal and frontal lobes (Kaas and Hackett, 1999). From these regions, two main processing streams emerge: Firstly, a dorsal component projects to inferior parietal and frontal areas, partly emerging from area Tpt, an important node in posterior auditory cortex. Secondly, there is a ventral component that runs anteriorly along the superior temporal lobe, reaching ventrolateral prefrontal areas (**Figure 2A**). The dorsal component performs time-dependent analyses of the stimulus and is involved in sound localization, while the ventral pathway is related to stimulus identification and has strong connectivity with the limbic, anterior temporal regions (Kaas and Hackett, 1999; Romanski, 2007; Rauschecker, 2012).

The dorsal pathway has been usually associated to the arcuate fasciculus (AF), but there are author differences in the definition of this tract (Catani et al., 2005; Rilling et al., 2008; Petrides, 2014). In this article, I will rely on Petrides' definition of the AF as "those monosynaptic axons that arch around the end of end of the lateral (Sylvian) fissure to link temporo-parietal cortex with frontal cortex" (Petrides, 2014 p. 163; see **Figure 2A**). Hodological studies in the monkey revealed three main components of this tract: one originating in the ventral superior temporal gyrus (STG) and the upper bank of the superior temporal sulcus (STS) that terminates in prefrontal area 44; another originating in the ventrocaudal STG, the adjacent STS and part of the medial temporal gyrus (MTG) that terminates in area 45; and a third branch originating from the dorsal STG that terminates in dorsolateral frontal cortex, the latter involved in auditory-related eye movements (for review see Petrides, 2014). Additional auditory-related connections have been described between posterior auditory regions and the ventral premotor cortex (Kumar et al., 2016), and between inferior parietal areas and the ventrolateral prefrontal cortex (Petrides, 2014), which will be discussed below.

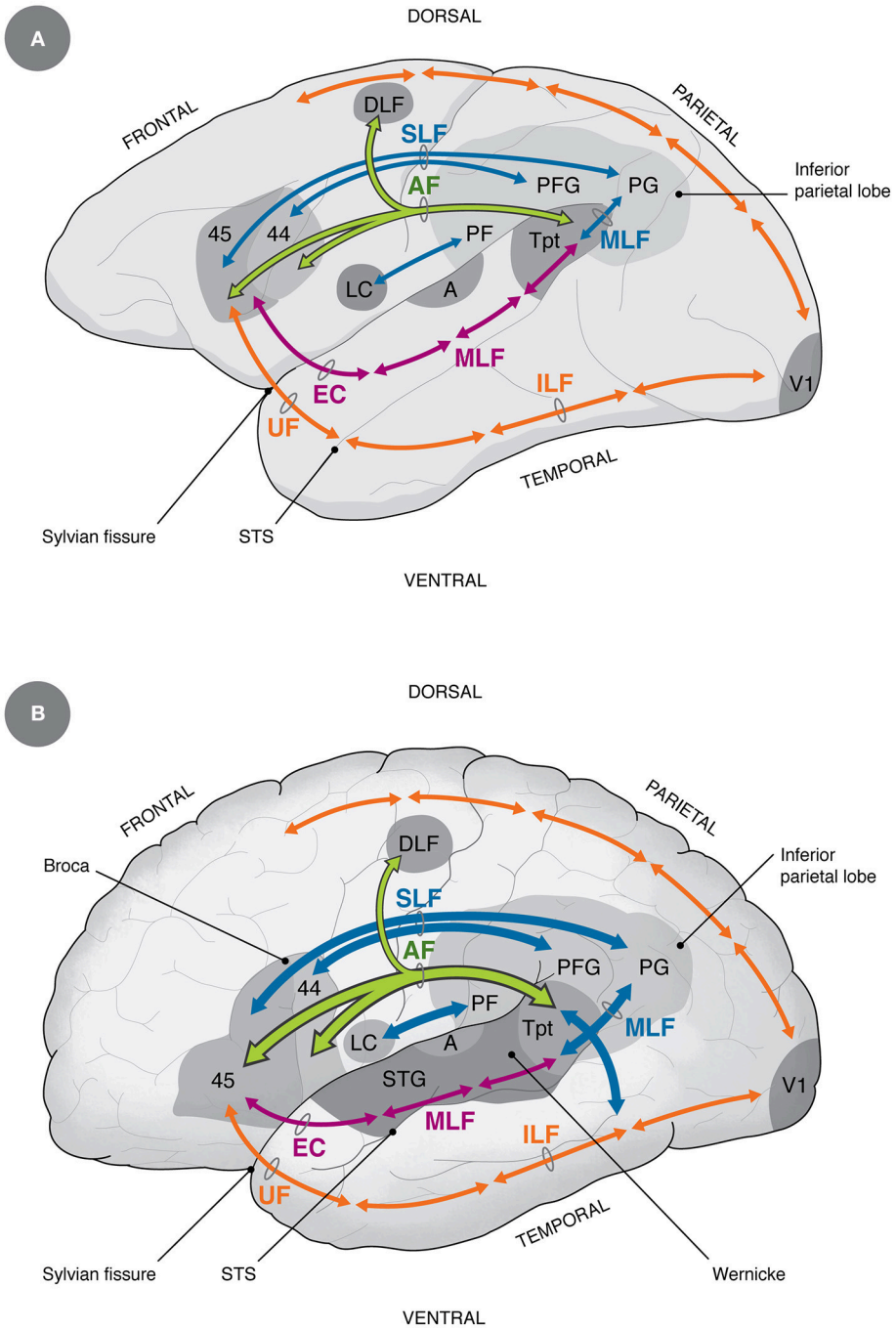


FIGURE 2 | Homology and differences in auditory-vocal cortical connectivity between non-human primates **(A)** and humans **(B)** (Petrides, 2014). The main differences between humans and non-human primates discussed in this paper refer to the increase in size of the AF, the ventral SLF and the posterior MLF (Rilling et al., 2008; Catani and Bambini, 2014; Stout and Hecht, 2017), the increase in connectivity between LC and inferior parietal areas (Kumar et al., 2016), the projection from the dorsal pathway into the medial temporal gyrus (additional blue arrow in humans), which is considered by some as part of the AF (Rilling et al., 2008; Catani and Bambini, 2014), and by others as part of the MLF (Petrides, 2014). Additional differences, not shown in the diagram, are that in humans there is a direct descending control of laryngeal motoneurons (Jürgens, 2009) and increased control of respiratory muscles (Belyk and Brown, 2017). A, primary auditory area; AF, arcuate fasciculus (green); DLF, dorsolateral frontal cortex; EC, extreme capsule; ILF, inferior longitudinal fasciculus (orange); LC, laryngeal and orofacial cortex; MLF, medial longitudinal fasciculus (magenta and blue); PF, PFG, PG, inferior parietal areas; SLF, ventral superior longitudinal fasciculus (blue); STG, superior temporal gyrus; Tpt, cytoarchitectonic area Tpt; UF, uncinate fasciculus; V1, primary visual area. For reference, dorsal and ventral visual pathways are shown in orange.

The subdivision into dorsal and ventral processing streams emulates the well-known organization of the visual system, containing a dorsal spatial-movement pathway that serves to coordinate actions along the superior parietal and frontal lobes, and a ventral pathway along the inferior temporal lobe and ventral-dorsolateral prefrontal cortex involved in visual identification of objects and faces (**Figure 2**; Goldman-Rakic, 1990, 1995). Interestingly, the ventral visual pathway, traveling along the inferior temporal lobe, projects to areas 47 and 45, partly overlapping with the termination of the auditory ventral pathway, and serving as a link between face and vocal perception (see below; Romanski, 2007).

In areas 12 and 45 of the monkey ventrolateral prefrontal cortex, single auditory neurons have been reported to respond to conspecific vocalizations, which are interspeded with visual neurons responding to conspecific faces (Romanski and Goldman-Rakic, 2002). Furthermore, some single neurons have been found to respond to both kinds of stimuli, and in some cases, these neurons suppress their activity when presented with an incongruous face-voice pair (Sugihara et al., 2006; Diehl and Romanski, 2014). Other studies have observed activity modulation of these neurons by both the emission and the perception of vocalizations, which is reminiscent of mirror neuron activity (Hage and Nieder, 2015). A different line of research has reported that perisylvian regions, including posterior parietal and ventrolateral prefrontal regions, activate during learning of simple artificial grammars and tasks similar to non-word sequencing tasks for humans (Milne et al., 2017; Wilson et al., 2017). These circuits overlap with those involved in syntactic processing in humans, suggesting that ordering and hierarchical processing of human speech and language partly derives from some domain-general mechanism for ordering actions.

THE SPEECH NETWORK IN HUMANS

The neural substrate for human speech has been analyzed since the times of Paul Broca and Karl Wernicke, who recognized two main speech-related cortical areas, an anterior one in the ventrolateral prefrontal cortex involved in speech production (Broca's area), and a posterior one in the posterior superior temporal lobe involved in speech perception (Wernicke's area). The AF has been classically considered to connect these areas, translating auditory representations into vocal articulatory patterns. This basic concept has been deeply revised in the last years, by virtue of evidence emerging from brain imaging studies depicting a complex network connecting several speech associated regions. In addition, Broca's and Wernicke's areas have been found to be less well defined anatomically than originally thought, and several surrounding regions may contribute to speech comprehension and execution (Fuertinger et al., 2015; Tremblay and Dick, 2016). By virtue of this evidence, a distinction has been made between a basic, or core language circuit, which is surrounded by a network of supporting areas (Fedorenko, 2014).

An Updated Model of the Language Regions

The current understanding of the basic speech circuit fits closely the organization of auditory networks in the monkey, including as a major component the direct connection between Broca's and Wernicke's areas via the AF (**Figure 2B**). This tract connects bidirectionally the core of Broca's area (Brodmann's areas 44 and 45), and the ventral premotor cortex according to some authors (Friederici, 2011), with regions of the posterior superior temporal lobe, including the ventral posterior STG, the posterior STS and part of the MTG (Rilling et al., 2008; Petrides, 2014; **Figure 2B**). The above mentioned area Tpt partly fits the termination of the AF, and has been considered by some as the core of Wernicke's region (Galaburda and Sanides, 1980). A related area is Spt, which is defined by functional activations during verbal working memory tasks. Since Tpt is defined cytoarchitectonically, and Spt is defined functionally, the relation between both regions is not yet clear, although they have been proposed to overlap (Hickok et al., 2003).

Beside the AF, there is a profuse connection between the ventrolateral prefrontal and premotor cortices on one side, and the inferior parietal lobe on the other, via the ventral SLF (Aboitiz and García, 1997; Petrides, 2014). This tract is termed by other authors as the anterior segment of the AF (Catani and Bambini, 2014). The inferior parietal lobe, also called Geschwind's area, is a multimodal region in which sensory modalities converge, and where mechanisms of motor program selection take place (Catani et al., 2005). Furthermore, the posterior segment of the middle longitudinal fasciculus (MLF, also termed the posterior segment of the AF) connects posterior auditory areas with the inferior parietal lobe, thus making up a triangular network with Broca's area, Wernicke's area and the inferior parietal lobe (Geschwind's area) at the respective vertices (Aboitiz and García, 1997; Catani et al., 2005; Catani and Bambini, 2014; Petrides, 2014; see **Figure 2A**). This circuit, together with the AF, has been dubbed the dorsal pathway, and is involved in sequential and structural analyses of phonology and grammar (at least complex, embedded grammatical forms). In addition to this projection, recent studies have unveiled a ventral language pathway, running along the superior temporal lobe and reaching the ventrolateral prefrontal cortex (specifically, areas 45 and 47) through the anterior temporal pole and the extreme capsule. This projection has been related to lexical and semantic linguistic processing (Saur et al., 2008; Catani and Bambini, 2014; Petrides, 2014), although other studies indicate involvement of the dorsal pathway in these functions as well (Rilling et al., 2012).

Analyses of resting state functional connectivity have shown that posterior Broca's area (area 44) correlates in activity with the posterior auditory cortex and anterior inferior parietal lobe, presumably via the AF and ventral SLF, and has said is considered to be involved in phonological and complex syntactic processing. This can be referred to as part of an auditory-vocal articulatory network, that is directly linked with premotor and motor regions controlling vocal and orofacial musculature (Petrides, 2014). On the other hand, anterior Broca's region (area 45) is functionally embedded in a multimodal network

involving the posterior inferior parietal cortex via the dorsal pathway (AF/SLF), and the anterior temporal lobe and STS via the ventral pathway, which interfaces with visual networks involved in stimulus identification and action processing (Binder and Desai, 2011; Friederici, 2011; Nelissen et al., 2011; Petrides, 2014; Beauchamp, 2015). This poses area 45 as a critical node linking the articulatory network with surrounding multimodal networks conveying lexico-semantic and syntactic information (Petrides, 2014).

Other brain systems involved in speech and language are subcortical nuclei like the cerebellum, basal ganglia, hippocampus and thalamus, which have extensive connections with the language-related cerebral cortex. Particularly, the cerebellum has closely coevolved with the cerebral cortex in mammals and primates (Herculano-Houzel, 2010), and there is growing evidence that it contributes not only to sensorimotor coordination of speech and sign language, but also to higher cognitive functions, participating in tasks requiring verbal working memory, verbal fluency and in general, phonological and semantic processing (Vias and Dick, 2017). Further research is strongly needed to unveil the specific participation of these structures in speech and language (see Aboitiz, 2017).

Lateralization of Speech

Although the left cerebral hemisphere is commonly said to be dominant for language, recent evidence has shown that speech perception and production are bilateral processes, with the right hemisphere specializing in low frequency syllabic sampling of the stimulus, and the left hemisphere specializing in high frequency phonemic processing (Hickok and Poeppel, 2007; Poeppel, 2014). Furthermore, prosody and music (in musically non-trained individuals) is better represented in the right hemisphere, and depends on both the dorsal and ventral pathways, where the dorsal pathway conveys categorization and motor control, and the ventral pathway is dedicated to sound analysis (Sammler et al., 2015). Prosody and syntax are highly tuned, which is relevant for making inflections and punctuating speech. The corpus callosum is needed for this synchronization, as revealed by the absence of a N-400-like evoked potential termed ELAN, that marks syntactic-prosodic incongruencies, in patients con lesions in the posterior but not the anterior corpus callosum, implicating parieto temporal areas in this interaction (Sammler et al., 2010).

Anatomically, the Sylvian fissure has different shapes in both hemispheres, being horizontal in the left hemisphere, and curving upwards to the parietal lobe in the right hemisphere (Aboitiz et al., 1992). Furthermore, the AF has been reported to be more robust in the left than in the right hemisphere since birth (Perani et al., 2011), while the ventral branch of the SLF shows the reverse asymmetry, being amplified in the right hemisphere (Budisavljevic et al., 2015). Whether the gross anatomical and tractographic asymmetries correlate with each other remains to be established. A recent study combining tractography and functional connectivity in a semantic decision task, found that the left AF is more robustly connected with the lateral temporal cortex in the left hemisphere, but with the inferior parietal lobe in the right hemisphere (Takaya et al., 2015). Nonetheless, a recent review indicates that there are some inconsistencies across studies when determining the asymmetry of the AF (Wilkinson et al., 2017).

From Auditory-Vocal to Speech Networks

As shown above, humans and monkeys display largely similar networks of auditory-prefrontal connectivity, indicating that the speech circuit emerged in evolution from a template existing in the last common ancestor. However, tractographic analyses revealed a significant difference in the development of the AF and ventral SLF, which are more robust, compared to the ventral pathway, in humans than in macaques (**Figure 2**; Aboitiz and García, 1997; Aboitiz et al., 2006a, 2010; Rilling et al., 2008, 2012; Aboitiz, 2012; Catani and Bambini, 2014; Petrides, 2014; Rilling, 2014). Nonetheless, tractographic evidence lacks the resolution of animal hodological techniques, and the separation of the AF from neighboring tracts can be problematic, especially as white matter becomes increasingly complex in larger brains (Petrides, 2014). The projection from the superior temporal lobe (Wernicke's region in the human) to the inferior parietal lobe (Geschwind's region) has been claimed to have strengthened in human evolution as well (Aboitiz and García, 1997; Aboitiz et al., 2006a; Catani and Bambini, 2014). Complying with these findings, the connectivity of the laryngeal motor cortex with inferior parietal areas was found to be as much as seven fold stronger in the human than in the macaque (Kumar et al., 2016). This projection may be indirectly connected with auditory projections to inferior parietal areas (Hickok, 2017). The strengthening of direct or indirect auditory-frontal connectivity via the dorsal pathway may have been achieved in more than one way. One is increasing the number of fibers connecting the respective regions, and a second one is changing the fiber composition and the tract integrity of the AF and related tracts, yielding enhanced functional connectivity. In this line, imaging analyses have revealed a weaker resting state functional connectivity between auditory and ventral prefrontal regions in the macaque than in the human (Mantini et al., 2011; Neubert et al., 2014; Petrides, 2014).

Nonetheless, comparative tractographic evidence suggests that the expansion of the dorsal pathway including the AF may have been gradual in primate evolution, as in the chimpanzee this component displays an amplification that is intermediate between the human and the monkey (Rilling et al., 2008). What functions does the chimpanzee AF subserve are an intriguing mystery, as like monkeys, apes are supposed to have limited vocal learning capacity. One possibility is that the AF of the chimpanzee participates in lip-sound associations, or more generally, orofacial control and its association to sound. Furthermore, while both the chimpanzee and the human share a projection between the auditory STG and the ventrolateral prefrontal cortex, only in humans there is a robust projection from the dorsal pathway, that ends in the multimodal STS and MTG (Rilling et al., 2008). There is discussion as to whether this component is part of the monosynaptic AF or whether it corresponds to fibers from the posterior MLF (Petrides, 2014; see **Figure 2**). Petrides (2014) also argues that the expansion of the temporoparietal junction of the human brain relative to other apes (Margulies et al., 2016), may have produced a ventral

displacement of areas located more dorsally in other primates, concomitant to a lengthening of the AF into the MTG. In this context, an interesting test would be to study the anatomy of the AF in microcephalic brains, who despite their small brain sizes, some still have linguistic abilities beyond those of language-trains chimpanzees. In any case, this descending component of the tract is undoubtedly part of the dorsal pathway that conveys multimodal information and may be involved in lexicosemantic and possibly grammatical processing (Rilling et al., 2008).

Non-human primates and especially chimpanzees, show brain asymmetry at the behavioral (for example, hand dominance), and gross anatomical and tractographic levels (specifically, they have a leftwardly asymmetrical AF) in auditory-vocal areas (Rilling et al., 2012). Nonetheless, functional and behavioral asymmetries are much more pronounced in humans than in other primates, and this might partly explain the consolidation of the speech circuit in the left hemisphere of most humans.

THE PHONOLOGICAL LOOP

Alan Baddeley (Baddeley and Hitch, 1974; Baddeley, 2007) proposed a model of working memory as a transient, limited capacity memory system that keeps information online, to be used in the near future. One of the components of this system is the phonological loop, a system involved in the transient maintenance of phonological sequences while performing a task. More than residing in a specific cortical region, the storage of phonological items in memory seems to depend on the sustained activation of a sensorimotor circuit encompassing posterior auditory areas (particularly, area Spt mentioned above) and the ventrolateral prefrontal cortex, in which the dorsal pathway may be a key element (Hickok, 2017). This mechanism is supported by inferior parietal regions that contribute attentional resources and select motor articulatory programs that transiently stabilize the phonological trace (Aboitiz, 2012, 2017; Rauschecker, 2012; Fedorenko, 2014).

A Key Innovation

Baddeley considered that the phonological loop did not evolve so much to process language, but rather to increase language learning capacity, and showed that verbal working memory in children is associated with their subsequent vocabulary acquisition (Baddeley, 2007). In this line, we have developed the hypothesis that the phonological loop is a character uniquely human among primates, that was crucial for the acquisition of speech in our species' early evolution. This process was accompanied by the development of auditory-vocal circuitry involving the AF and other components of the dorsal pathway, together with the increasing descending control over vocal cranial motor nuclei (Aboitiz and García, 1997; Aboitiz et al., 2006a, 2010; Aboitiz, 2012, 2017; see also Catani and Bambini, 2014).

Supporting this proposal, there is evidence that points to an increased auditory-vocal anatomical and functional connectivity via the dorsal pathway in humans compared to monkeys (see above), and behavioral experiments have shown that as opposed to visual memory, monkeys are strongly limited in auditory long and short term memory (Scott et al., 2012; Scott and Mishkin, 2016). Furthermore, tractographic integrity of the AF has been associated with verbal working memory, verbal fluency and sentence comprehension in humans, and its development in childhood correlates with increasing language abilities (Yeatman et al., 2011; Skeide et al., 2016; Schomers et al., 2017). Certainly, other mechanisms beside working memory capacity were involved in the origin of speech at its different levels, but the argument is that the phonological loop facilitated these acquisitions.

The Phonological Loop Amplified

Verbal working memory is not unitary, and operates at very different levels, phonological, syntactic, lexical, and semantic (Caplan and Waters, 1999). These levels depend on different but highly interacting neural networks, as for example phonological working memory relies on the dorsal pathway and the AF (Schomers et al., 2017), while lexicosemantic working memory depends more, but not exclusively, on the ventral pathway, in compliance with the organization of the auditory system (Binder and Desai, 2011). Syntactic working memory, especially complex, embedded grammatical forms, has been proposed to depend on the dorsal pathway (Friederici, 2011; Goucha et al., 2017). Nonetheless, some syntactic processes have been found to depend on the ventral pathway, especially when involving interpretation of meaningful discourse (Griffiths et al., 2013).

How did this complex set of networks evolve? I will propose here a sequence of five overlapping stages in the evolution and amplification of the auditory-vocal circuitry in the human lineage. Firstly, like other primates, early australopithecines possibly relied more intensely on the ventral auditory pathway to process vocalizations and associating them to visual stimuli representing faces and gestures in the anterior ventrolateral prefrontal cortex (Romanski, 2007). Secondly, a main innovation was the increased neural control of vocalizations and orofacial movements via the laryngeal and orofacial motor cortex, directly connected both to brainstem motor nuclei and inferior parietal areas (Kumar et al., 2016; Hickok, 2017). Thirdly, atop of this basic circuit, the activation of an auditory-vocal reciprocal loop, relying on a bidirectional connection between Broca's region with posterior auditory areas via the AF and ventral SLF, enabled the learning of complex vocal utterances by imitation, establishing the basic components of the phonological loop and enhancing auditory-vocal working memory capacity (Petrides, 2014). For example, in a phonological working memory task using multisyllabic pseudowords, the areas activated during maintenance of the stimulus on mind were posterior temporal area Spt (see above) and the nearby posterior STS, where the integration of phonemes into word forms takes place. While the posterior STS has been related to the AF (Petrides, 2014), the connectivity of area Spt remains to be determined. This circuit is the core network for vocal articulation, and its functional amplification is probably a key development in the human lineage, allowing early humans to learn increasingly complex phonological, or pre-phonological sequences. This may have been used initially for social bonding, but perhaps also for transmitting simple information about events or

objects, as in vervet monkey alarm calls that signal specific predators. The structure of vervet alarm calls is largely innate, but their referentials or "meanings" are dependent on social experience (Seyfarth et al., 1980). In early humans, these vocal calls may have become learned by virtue of increasing vocal plasticity. As the vocal messages became increasingly complex, more extended cortical regions became recruited, particularly inferior parietal regions projecting to Broca's area, that also provided a rudimentary order to the sequences of vocalizations, possibly relying on constraints associated with sensorimotor programming.

In a fourth event, the ventral auditory pathway, processing the sound characteristics of vocalizations, strengthened associations with the ventral visual pathway via the STS, where information about objects, events and actions is processed (García et al., 2014). In addition, the development of a dorsal pathway projection to the MTG in humans but not in apes may have contributed to transmit lexical-semantic information and possibly some elements of syntax into the dorsal pathway (Rilling et al., 2008). The auditory ventral pathway is heavily connected with anterior Broca's area and neighboring regions (areas 45 and 47), which integrates articulatory information from the dorsal stream with auditory-lexical inputs from the ventral stream, facilitating the transformation of phonological representations into vocal motor programs (Skeide and Friederici, 2016). As associations between learned vocalizations and visual representations, originating along the STS, became conventionalized by cultural or proto-cultural development, a primitive lexicon appeared, providing meaning to the phonological sequences and slowly forming a proto-lexicon (García et al., 2014). This early, proto-lexical stage may have lasted for a long time, while modern speech and grammar are probably more recent acquisitions (Bickerton, 2014). For reasons of space, it is impossible to discuss the emergence of grammar in this article, but I have argued elsewhere that syntactic rules appeared to translate complex visuomotor representations of actions and events into hierarchical phonological structures and vice versa (Aboitiz et al., 2006b; Aboitiz, 2017, in press). This perspective differs from the canonical view of grammar as an encapsulated device, separate from other cognitive systems (Hauser et al., 2002).

DISCUSSION: A BRIEF SCENARIO OF SPEECH ORIGINS

This review has provided comparative anatomical, behavioral, and functional evidence that in my view points to a continuous evolution of the vocal system and its neural control, from non-human primate vocalizations to at least the early stages of human speech. On the other hand, exponents of the mirror system hypothesis tend to disregard the role of non-human primate vocalizations, and especially downplay the emergence of prosody in the origin of speech. What comes below is a tentative scenario of early human evolution, in which speech evolved as a response to selective forces that resulted in both biological and cultural adaptations to yield modern language.

Australopithecines originated some 4 million years ago, and underwent a quite different evolutionary trajectory than that of their ancestors and sister taxa. These were successful bipedal species, with an ecology and social organization probably similar to that of macaques living in open spaces (Meindl et al., 2018). Australopithecine descendants, belonging to the genus *Homo*, probably developed a quite intense social life compared to other primates, concomitant with increased levels of prosocial neurotransmitters in the subcortical basal ganglia (Raghanti et al., 2018). In addition, early humans developed a culture in which tool making and fire control became essential elements (although these may have started already in Australopithecines), mainly due to a highly sophisticated digital dexterity, possibly far beyond that found in other primates. In addition to this, I propose that Australopithecines and early *Homo* communicated intensely with vocal signals. Darwin already proposed that initially, vocal communication was more similar to music than to speech, which has been updated as the "musical protolanguage," or prosodic hypothesis (Fitch, 2010; Hickok, 2017). Early humans probably engaged in turn-taking conversations that may have lasted for a long time and served to strengthen bonds, especially between mother and child, but also to communicate emotional states, as seen in marmoset monkeys (Takahashi et al., 2013, 2016). Other non-primate examples are highly social mammals like cetaceans, who use learned vocalizations to promote social bonds and group coordination (King and McGregor, 2016). Each individual dolphin in a group has its own specific vocalization that has been learned from early life (King et al., 2016). Cetaceans, similarly to elephants, orangutans and other highly social mammals, have been shown to be able to imitate the human voice (Ridgway et al., 2012; Stoeger et al., 2012; Lameira et al., 2016; Abramson et al., 2018). Supporting this perspective, increasing vocal complexity has been associated with more elaborate social behavior in birds, where cooperative breeding correlates with vocal richness. This is consistent with the idea that social complexity by itself may be a selective force driving vocal evolution (Leighton, 2017). Australopithecines had brains not much larger than those of chimpanzees, and the expansion of human brain size does not take place until later. Yet, acquisition of vocal plasticity does not require a large brain, as can be shown by the example of echolocating bats, who are highly social and good vocal learners (Morell, 2014). Probably, brain size increased concomitant with the progressive development of linguistic and social skills, as there was increasing cognitive pressure with the more complex communication and social life that was emerging (Aboitiz, 2017).

Nonetheless, early human communication was probably multimodal, using both vocalizations and gestures, as it is today. The vocal learning skills of early humans may have been put to use to mimic the sounds of animals, water, the wind, or other elements nearby, together with gestural pantomime (García et al., 2014). Likewise, they may have developed learned alarm calls that signal specific predators, that were accompanied by gesticulations (Seyfarth et al., 1980). This emerged into a primitive, gestural-vocal proto-semantic system (García et al., 2014). However, pantomimes and manual gestures probably never went much beyond the stage observed in normally

speaking modern humans. On the other hand, the elaboration of auditory-vocal networks and the gradual consolidation of the phonological loop eventually enabled our ancestors to start communicating increasingly complex meanings through the voice (García et al., 2014; Aboitiz, 2017). In later stages, the acquisition of semantics and a primitive lexicon may have been essential for the separation between both kinds of expression, and possibly contributed to the lateralization of these functions, with phonology and speech on the left hemisphere and music/prosody in the right hemisphere, both communicating via the corpus callosum (Sammler et al., 2015).

For these events to occur, a tight control of lips, tongue and the vocal folds must have taken place. Furthermore, a precise coordination between the vocal folds and the upper vocal tract may have evolved in these species, to synchronize vocalizations with mouth movements, as is seen in gelada baboons (Ghazanfar and Takahashi, 2014a). The development of direct cortical control of these brainstem nuclei was most likely not a difficult evolutionary step, that could have been achieved with minimal genetic changes (Gu et al., 2017), and may have also developed together with increasing cortical size (Herculano-Houzel et al., 2016). For our ancestors and not for other primates, there was a strong selective benefit in developing vocal learning capacity, possibly in the context of an increasingly complex social organization.

Summarizing, it was intense sociality, together with a tool-making culture and specific ecological circumstances, that selected for more complex vocalization and gestural capacity, generating a virtuous cycle that eventually exploded as a functional phonological loop gradually consolidated in our recent ancestors. Furthermore, human brain size increased in response to pressure for increasing communication and technological abilities, where larger brains enabled more complex communication and behavioral innovations, generating further communicative and cognitive pressures (Bickerton, 2014; Aboitiz, 2017). This virtuous cycle may have had an exponential dynamics, being quite slow for a long time, until a threshold was reached that launched human behavior into modern language. While we will probably never know exactly which circumstances led to the acquisition of speech nor when it happened, this article has aimed to show evidence for strong homology between the auditory-vocal neural circuitry in humans and non-human primates.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

ACKNOWLEDGMENTS

Special thanks to Isabel Guerrero for producing the illustrations, and thanks to the reviewers and editor of this article for their insightful comments. This research was supported in part by FONDECYT Grant 1160258.

REFERENCES

Aboitiz, F. (1995). Working memory networks and the origin of language areas in the human brain. *Med. Hypoth.* 44, 504–506. doi: 10.1016/0306-9877(95)90514-6

Aboitiz, F. (2012). Gestures, vocalizations, and memory in language origins. *Front. Evol. Neurosci.* 4:2. doi: 10.3389/fnevo.2012.00002

Aboitiz, F. (2013). How did vocal behavior "take over" the gestural communication system? *Lang. Cogn.* 5, 167–176. doi: 10.1515/langcog-2013-0011

Aboitiz, F. (2017). *A Brain for Speech. A View From Evolutionary Neuroanatomy.* London: Palgrave Macmillan.

Aboitiz, F. (in press). Voice, gesture and working memory in the emergence of speech. *Interact. Stud.*

Aboitiz, F., García, R., Brunetti, E., and Bosman,. C. (2006b). "The origin of Broca's area from an ancestral working memory network," in *Broca's Region*, eds Y. Grodzinsky and K. Amunts (Oxford: Oxford University Press), 3–16.

Aboitiz, F., Aboitiz, S., and García, R. (2010). The phonological loop: a key innovation in human evolution. *Curr. Anthropol.* 51, S55–S65. doi: 10.1086/650525

Aboitiz, F., and García, R. (1997). The evolutionary origin of the language areas in the human brain. a neuroanatomical perspective. *Brain Res. Rev.* 25, 381–396. doi: 10.1016/S0165-0173(97)00053-2

Aboitiz, F., García, R. R., Bosman, C., and Brunetti, E. (2006a). Cortical memory mechanisms and language origins. *Brain Lang.* 98, 40–56. doi: 10.1016/j.bandl.2006.01.006

Aboitiz, F., Scheibel, A. B., and Zaidel, E. (1992). Morphometry of the Sylvian fissure and the corpus callosum, with emphasis on sex differences. *Brain* 115, 1521–1541. doi: 10.1093/brain/115.5.1521

Abramson, J. Z., Hernández-Lloreda, M. V., García, L., Colmenares, F., Aboitiz, F., and Call, J. (2018). Imitation of novel conspecific and human speech sounds in the killer whale (*Orcinus orca*). *Proc. R. Soc. B.* 285:20172171. doi: 10.1098/rspb.2017.2171

Arbib, M. A. (2012). *How the Brain Got Language. The Mirror System Hypothesis.* Oxford: Oxford University Press.

Baddeley, A. (2007). *Working Memory, Thought and Action.* Oxford: Oxford University Press.

Baddeley, A. D., and Hitch, G. J. (1974). "Working memory," in *Recent Advances in Learning and Motivation*, Vol. 8, ed G. A. Bower (New York, NY: Academic Press), 47–89.

Balzeau, A., Gilissen, E., Holloway, R. L., Prima, S., and Grimaud-Hervé, D. (2014). Variations in size, shape and asymmetries of the third frontal convolution in hominids: paleoneurological implications for hominin evolution and the origin of language. *J. Hum. Evol.* 76, 116–128. doi: 10.1016/j.jhevol.2014.06.006

Beauchamp, M. S. (2015). The social mysteries of the superior temporal sulcus. *Trends Cogn. Sci.* 19, 489–490. doi: 10.1016/j.tics.2015.07.002

Belyk, M., and Brown, S. (2017). The origins of the vocal brain in humans. *Neurosci. Biobehav. Rev.* 77, 177–193. doi: 10.1016/j.neubiorev.2017.03.014

Bickerton, D. (2014). *More Than Nature Needs. Language, Mind, and Evolution.* Cambridge: Harvard University Press.

Binder, J. R., and Desai, R. H. (2011). The neurobiology of semantic memory. *Trends Cogn. Sci.* 15, 527–536. doi: 10.1016/j.tics.2011.10.001

Boë, L. J., Berthommier, F., Legou, T., Captier, G., Kemp, C., Sawallis, T. R., et al. (2017). Evidence of a vocalic Proto-system in the Baboon (*Papio papio*) suggests Pre-hominin speech precursors. *PLoS ONE* 12:e0169321. doi: 10.1371/journal.pone.0169321

Borra, E., Gerbella, M., Rozzi, S., and Luppino, G. (2017). The macaque lateral grasping network: a neural substrate for generating purposeful hand actions. *Neurosci. Biobehav. Rev.* 75, 65–90. doi: 10.1016/j.neubiorev.2017.01.017

Bosman, C., López, V., and Aboitiz, F. (2005). Sharpening Occam's razor: is there necessity of a hand-signing stage prior to vocal communication? *Behav. Brain Sci.* 28, 128–129. doi: 10.1017/S0140525X05250033

Bruner, E. (2017). Language, paleoneurology, and the fronto-parietal system. *Front Hum. Neurosci.* 11:349. doi: 10.3389/fnhum.2017.00349

Bruner, E., and Holloway, R. L. (2010). A bivariate approach to the widening of the frontal lobes in the genus *Homo*. *J. Hum. Evol.* 58, 138–146. doi: 10.1016/j.jhevol.2009.10.005

Bruner, E., De La Cuétara, J. M., and Holloway, R. (2011). A bivariate approach to the variation of the parietal curvature in the genus *Homo*. *Anat. Rec.* 294, 1548–1556. doi: 10.1002/ar.21450

Bruner, E., de la Cuétara, J. M., Masters, M., Amano, H., and Ogihara, N. (2014). Functional craniology and brain evolution: from paleontology to biomedicine. *Front. Neuroanat.* 8:19. doi: 10.3389/fnana.2014.00019

Budisavljevic, S., Dell'Acqua, F., Rijsdijk, F. V., Kane, F., Picchioni, M., McGuire, P., et al. (2015). Age-related differences and heritability of the Perisylvian language networks. *J. Neurosci.* 35, 12625–12634. doi: 10.1523/JNEUROSCI.1255-14.2015

Caplan, D., and Waters, G. S. (1999). Verbal working memory and sentence comprehension. *Behav. Brain Sci.* 22, 77–94. doi: 10.1017/S0140525X99001788

Cataldo, D. M., Migliano, A. B., and Vinicius, L. (2018). Speech, stone tool-making and the evolution of language. *PLoS ONE* 13:e0191071. doi: 10.1371/journal.pone.0191071

Catani, M., and Bambini, V. (2014). A model for social communication and language evolution and development (SCALED). *Curr. Opin. Neurobiol.* 28, 165–171. doi: 10.1016/j.conb.2014.07.018

Catani, M., Jones, D. K., and ffytche. D. H. (2005). Perisylvian language networks of the human brain. *Ann. Neurol.* 57, 8–16. doi: 10.1002/ana.20319

Catani, M., Mesulam, M. M., Jakobsen, E., Malik, F., Martersteck, A., Wieneke, C., et al. (2013). A novel frontal pathway underlies verbal fluency in primary progressive aphasia. *Brain* 136, 2619–2628. doi: 10.1093/brain/awt163

Cook, R., Bird, G., Catmur, C., Press, C., and Heyes, C. (2014). Mirror neurons: from origin to function. *Behav. Brain Sci.* 37, 177–192. doi: 10.1017/S0140525X13000903

Coudé, G., and Ferrari, P. F. (in press). Reflections on the organization of the cortical motor system and its role in evolution of communication in primates. *Interact. Stud.*

Coudé, G., Ferrari, P. F., Rodà, F., Maranesi, M., Borelli, E., Veroni, V., et al. (2011). Neurons controlling voluntary vocalization in the macaque ventral premotor cortex. *PLoS ONE* 6:e26822. doi: 10.1371/journal.pone.0026822

di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., and Rizzolatti, G. (1992). Understanding motor events: a neurophysiological study. *Exp. Brain Res.* 91, 176–180. doi: 10.1007/BF00230027

Diehl, M. M., and Romanski, L. M. (2014). Responses of prefrontal multisensory neurons to mismatching faces and vocalizations. *J. Neurosci.* 34, 11233–11243. doi: 10.1523/JNEUROSCI.5168-13.2014

Fedorenko, E. (2014). The role of domain-general cognitive control in language comprehension. *Front. Psychol.* 5:335. doi: 10.3389/fpsyg.2014.00335

Ferrari, P. F. F., Gerbella, M., Coudé, G., and and Rozzi, S. (2017). Two different mirror neuron networks: the sensorimotor (hand) and limbic (face) pathways. *Neuroscience* 358, 300–315. doi: 10.1016/j.neuroscience.2017.06.052

Ferrari, P. F., Gallese, V., Rizzolatti, G., and Fogassi, L. (2003). Mirror neurons responding to the observation of ingestive and communicative mouth actions in the monkey ventral premotor cortex. *Eur. J. Neurosci.* 17, 1703–1714. doi: 10.1046/j.1460-9568.2003.02601.x

Fitch, W. T. (2010). *The Evolution of Language*. Cambridge: Cambridge University Press.

Fitch, W. T., and Reby, D. (2001). The descended larynx is not uniquely human. *Proc. Biol. Sci.* 268, 1669–1675. doi: 10.1098/rspb.2001.1704

Fitch, W. T., de Boer, B., Mathur, N., and Ghazanfar, A. A. (2017). Response to Lieberman on "Monkey vocal tracts are speech-ready". *Sci. Adv.* 3:e1701859. doi: 10.1126/sciadv.1701859

Fitch, W. T., de Boer, B., Mathur, N., and Ghazanfar, A. A. (2016). Monkey vocal tracts are speech-ready. *Sci. Adv.* 2:e1600723. doi: 10.1126/sciadv.1600723

Fleagle, J. C. (2013). *Primate Adaptation and Evolution*, *3rd Edn.* New York, NY: Academic Press.

Friederici, A. D. (2011). The brain basis of language processing: from structure to function. *Physiol. Rev.* 91, 1357–1392. doi: 10.1152/physrev.00006.2011

Fuertinger, S., Horwitz, B., and Simonyan, K. (2015). The functional connectome of speech control. *PLoS Biol.* 13:e1002209. doi: 10.1371/journal.pbio.1002209

Galaburda, A., and Sanides, F. (1980). Cytoarchitectonic organization of the human auditory cortex. *J. Comp. Neurol.* 190, 597–610.

García, R. R., Zamorano,. F., and Aboitiz, F. (2014). From imitation to meaning: circuit plasticity and the acquisition of a conventionalized semantics. *Front. Hum. Neurosci.* 8:605. doi: 10.3389/fnhum.2014.00605

Geissmann, T. (2002). Duet-splitting and the evolution of gibbon songs. *Biol. Rev. Camb. Philos. Soc.* 77, 57–76. doi: 10.1017/S1464793101005826

Ghazanfar, A. A., and Rendall, D. (2008). Evolution of human vocal production. *Curr. Biol.* 18, R457–R460. doi: 10.1016/j.cub.2008.03.030

Ghazanfar, A. A., and Takahashi, D. Y. (2014a). The evolution of speech: vision, rhythm, cooperation. *Trends Cogn. Sci.* 18, 543–553. doi: 10.1016/j.tics.2014.06.004

Ghazanfar, A. A., and Takahashi, D. Y. (2014b). Facial expressions and the evolution of the speech rhythm. *J. Cogn. Neurosci.* 26, 1196–1207. doi: 10.1162/jocn_a_00575

Ghazanfar, A. A., Takahashi, D. Y., Mathur, N., and Fitch, W. T. (2012). Cineradiography of monkey lip-smacking reveals putative precursors of speech dynamics. *Curr. Biol.* 22, 1176–1182. doi: 10.1016/j.cub.2012.04.055

Goldman-Rakic, P. S. (1995). Cellular basis of working memory. *Neuron* 14, 477–485. doi: 10.1016/0896-6273(95)90304-6

Goldman-Rakic, P. S. (1990). Cellular and circuit basis of working memory in prefrontal cortex of non-human primates. *Prog. Brain Res.* 85, 325–335. doi: 10.1016/S0079-6123(08)62688-6

Goucha, T., Zaccarella, E., and Friederici, A. D. (2017). A revival of the *Homo* loquens as a builder of labeled structures: neurocognitive considerations. *Neurosci. Biobehav. Rev.* 81, 213–224. doi: 10.1016/j.neubiorev.2017.01.036

Griffiths, J. D., Marslen-Wilson, W. D., Stamatakis, E. A., and Tyler, L. K. (2013). Functional organization of the neural language system: dorsal and ventral pathways are critical for syntax. *Cereb. Cortex* 23, 139–147. doi: 10.1093/cercor/bhr386

Gu, Z., Kalambogias, J., Yoshioka, S., Han, W., Li, Z., Kawasawa, Y. I., et al. (2017). Control of species-dependent cortico-motoneuronal connections underlying manual dexterity. *Science* 357, 400–404. doi: 10.1126/science.aan3721

Hage, S. R., and Nieder, A. (2013). Single neurons in monkey prefrontal cortex encode volitional initiation of vocalizations. *Nat. Commun.* 4, 2409. doi: 10.1038/ncomms3409

Hage, S. R., and Nieder, A. (2015). Audio-vocal interaction in single neurons of the monkey ventrolateral prefrontal cortex. *J. Neurosci.* 35, 7030–7040. doi: 10.1523/JNEUROSCI.2371-14.2015

Hage, S. R., and Nieder, A. (2016). Dual neural network model for the evolution of speech and language. *Trends Neurosci.* 39, 813–829. doi: 10.1016/j.tins.2016.10.006

Hage, S. R., Gavrilov, N., and Nieder, A. (2013). Cognitive control of distinct vocalizations in rhesus monkeys. *J. Cogn. Neurosci.* 25, 1692–1701. doi: 10.1162/jocn_a_00428

Hage, S. R., Gavrilov, N., and Nieder, A. (2016). Developmental changes of cognitive vocal control in monkeys. *J. Exp. Biol.* 219, 1744–1749. doi: 10.1242/jeb.137653

Hauser, M. D., Chomsky, N., and Fitch, W. T. (2002). The faculty of language: what is it, who has it, and how did it evolve? *Science* 298, 1569–1579. doi: 10.1126/science.298.5598.1569

Hecht, E. E., Gutman, D. A., Bradley, B. A., Preuss, T. M., and Stout, D. (2015). Virtual dissection and comparative connectivity of the superior longitudinal fasciculus in chimpanzees and humans. *Neuroimage* 108, 124–137. doi: 10.1016/j.neuroimage.2014.12.039

Herculano-Houzel, S. (2010). Coordinated scaling of cortical and cerebellar numbers of neurons. *Front. Neuroanat.* 4:12. doi: 10.3389/fnana.2010.00012

Herculano-Houzel, S., Catania, K., Manger, P. R., and Kaas, J. H. (2015). Mammalian brains are made of these: a dataset of the numbers and densities of neuronal and non-neuronal cells in the brain of glires, primates, scandentia, eulipotyphlans, afrotherians and artiodactyls, and their relationship with body mass. *Brain Behav. Evol.* 86, 145–163. doi: 10.1159/000437413

Herculano-Houzel, S., Kaas, J. H., and de Oliveira-Souza, R. (2016). Corticalization of motor control in humans is a consequence of brain scaling in primate evolution. *J. Comp. Neurol.* 524, 448–455. doi: 10.1002/cne.23792

Hickok, G. (2014). *The Myth of Mirror Neurons: The Real Neuroscience of Communication and Cognition.* New York, NY: Norton Press.

Hickok, G. (2017). A cortical circuit for voluntary laryngeal control: implications for the evolution language. *Psychon. Bull. Rev.* 24, 56–63. doi: 10.3758/s13423-016-1100-z

Hickok, G., and Poeppel, D. (2007). The cortical organization of speech processing. *Nat. Rev. Neurosci.* 8, 393–402. doi: 10.1038/nrn2113

Hickok, G., Buchsbaum, B., Humphries, C., and Muftuler, T. (2003). Auditory-motor interaction revealed by fMRI: speech, music, and working memory in area Spt. *J. Cogn. Neurosci.* 15, 673–682. doi: 10.1162/0898929033223 07393

Holloway, R. L. (ed.). (2017). "Endocasts," in *Reference Module in Neuroscience and Biobehavioral Psychology* (New York, NY: Elsevier), 1–19.

Holstege, G., and Subramanian, H. H. (2016). Two different motor systems are needed to generate human speech. *J. Comp. Neurol.* 524, 1558–1577. doi: 10.1002/cne.23898

Jürgens, U. (2009). The neural control of vocalization in mammals: a review. *J. Voice* 23, 1–10. doi: 10.1016/j.jvoice.2007.07.005

Kaas, J. H., and Hackett, T. A. (1999). 'What' and 'where' processing in auditory cortex. *Nat. Neurosci.* 2, 1045–1047. doi: 10.1038/15967

King, S. L., and McGregor, P. K. (2016). Vocal matching: the what, the why and the how. *Biol. Lett.* 12:20160666. doi: 10.1098/rsbl.2016.0666

King, S. L., Guarino, E., Keaton, L., Erb, L., and Jaakkola, K. (2016). Maternal signature whistle use aids mother-calf reunions in a bottlenose dolphin, *Tursiops truncatus. Behav. Process.* 126, 64–70. doi: 10.1016/j.beproc.2016.03.005

Koda,. H., Lemasson, A., Oyakawa, C., Rizaldi, P., Amungkas, J., and Masataka, N. (2013). Possible role of mother-daughter vocal interactions on the development of species-specific song in gibbons. *PLoS ONE* 8:e71432. doi: 10.1371/journal.pone.0071432

Kohler, E., Keysers, C., Umiltá, M. A., Fogassi, L., Gallese, V., and Rizzolatti, G. (2002). Hearing sounds, understanding actions: action representation in mirror neurons. *Science* 297, 846–848. doi: 10.1126/science.1070311

Kumar, V., Croxson, P. L., and Simonyan, K. (2016). Structural organization of the laryngeal motor cortical network and its implication for evolution of speech production. *J. Neurosci.* 36, 4170–4181. doi: 10.1523/JNEUROSCI.3914-15.2016

Lameira, A. R., Hardus, M. E., Mielke, A., Wich, S. A., and Shumaker, R. W. (2016). Vocal fold control beyond the species-specific repertoire in an orangutan. *Sci. Rep.* 6:30315. doi: 10.1038/srep30315

Lameira, A. R., Maddieson, I., and Zuberbühler, K. (2014). Primate feedstock for the evolution of consonants. *Trends Cogn. Sci.* 18, 60–62. doi: 10.1016/j.tics.2013.10.013

Leighton, G. M. (2017). Cooperative breeding influences the number and type of vocalizations in avan lineages. *Proc. Roy. Soc. Lond. B* 284:20171508. doi: 10.1098/rspb.2017.1508.

Lieberman, P. (1968). Primate vocalizations and human linguistic ability. *J. Acoust. Soc. Am.* 44, 1574–1584. doi: 10.1121/1.1911299

Lieberman, P. (2017). Comment on "Monkey vocal tracts are speech-ready". *Sci. Adv.* 3:e1700442. doi: 10.1126/sciadv.1700442

Mantini, D., Gerits, A., Nelissen, K., Durand, J. B., Joly, O., Simone, L., et al. (2011). Default mode of brain function in monkeys. *J. Neurosci.* 31, 12954–12962. doi: 10.1523/JNEUROSCI.2318-11.2011

Margulies, D. S., Ghosh, S. S., Goulas, A., Falkiewicz, M., Huntenburg, J. M., Langs, G., et al. (2016). Situating the default-mode network along a principal gradient of macroscale cortical organization. *Proc. Natl. Acad. Sci. U.S.A.* 113, 12574–12579. doi: 10.1073/pnas.1608282113

Meindl, R. S., Chaney, M. E., and Lovejoy, C. O. (2018). Early hominids may have been weed species. *Proc. Natl. Acad. Sci. U.S.A.* 115, 1244–1249. doi: 10.1073/pnas.1719669115

Milne, A. E., Petkov, C. I., and Wilson, B. (2017). Auditory and visual sequence learning in humans and monkeys using an artificial grammar learning paradigm. *Neuroscience.* doi: 10.1016/j.neuroscience.2017.06.059. [Epub ahead of print].

Morell, V. (2014). When the bat sings. *Science* 344, 1334–1337. doi: 10.1126/science.344.6190.1334

Morgan, T. J., Uomini, N. T., Rendell, L. E., Chouinard-Thuly, L., Street, S. E., Lewis, H. M., et al. (2015). Experimental evidence for the co evolution of hominin tool-making teaching and language. *Nat. Commun.* 6, 6029. doi: 10.1038/ncomms7029

Morrill, R. J., Paukner, A., Ferrari, P. F., and Ghazanfar, A. A. (2012). Monkey lipsmacking develops like the human speech rhythm. *Dev. Sci* .15, 557–568. doi: 10.1111/j.1467-7687.2012.01149.x

Mundinano, I. C., Fox, D. M., Kwan, W. C., Vidaurre, D., Teo, L., Homman-Ludiye, J., et al. (2018). Transient visual pathway critical for normal development of primate grasping behavior. *Proc. Natl. Acad. Sci. U.S.A.* 115, 1364–1369. doi: 10.1073/pnas.1717016115

Nelissen, K., Borra, E., Gerbella, M., Rozzi, S., Luppino, G., Vanduffel, W., et al. (2011). Action observation circuits in the macaque monkey cortex. *J. Neurosci.* 31, 3743–3756. doi: 10.1523/JNEUROSCI.4803-10.2011

Neubauer, S., Hublin, J.-J., and Gunz, P. (2018). The evolution of modern human brain shape. *Science Adv.* 4:aao5961. doi: 10.1126/sciadv.aao5961.

Neubert, F. X., Mars, R. B., Thomas, A. G., Sallet, J., and Rushworth, M. F. (2014). Comparison of human ventral frontal cortex areas for cognitive control and language with areas in monkey frontal cortex. *Neuron* 81, 700–713. doi: 10.1016/j.neuron.2013.11.012

Nummela, S. U., Jovanovic, V., de la Mothe, L., and Miller, C. T. (2017). Social context-dependent activity in marmoset frontal cortex populations during natural conversations. *J. Neurosci.* 37, 7036–7047. doi: 10.1523/JNEUROSCI.0702-17.2017

Perani, D., Saccuman, M. C., Scifo, P., Anwander, A., Spada, D., Baldoli, C., et al. (2011). Neural language networks at birth. *Proc. Natl. Acad. Sci. U.S.A.* 108, 16056–16061. doi: 10.1073/pnas.1102991108

Pereira-Pedro, A. S., Rilling, J. K., Chen, X., Preuss, T. M., and Bruner, E. (2017). Midsagittal brain variation among non-human primates: insights into evolutionary expansion of the human precuneus. *Brain Behav. Evol.* 90, 255–263. doi: 10.1159/000481085

Petkov, C. I., and Jarvis, E. D. (2012). Birds, primates, and spoken language origins: behavioral phenotypes and neurobiological substrates. *Front. Evol. Neurosci.* 4:12. doi: 10.3389/fnevo.2012.00012

Petrides, M. (2014). *Neuroanatomy of Language Regions of the Human Brain.* New York, NY: Academic Press.

Petrides, M., Cadoret, G., and Mackey, S. (2005). Orofacial somatomotor responses in the macaque monkey homologue of Broca's area. *Nature* 435, 1235–1238. doi:10.1038/nature03628

Pisanski, K., Cartei, V., McGettigan, C., Raine, J., and Reby, D. (2016). Voice modulation: a window into the origins of human vocal control? *Trends Cogn. Sci.* 20, 304–318. doi: 10.1016/j.tics.2016.01.002

Poeppel, D. (2014). The neuroanatomic and neurophysiological infrastructure for speech and language. *Curr. Opin. Neurobiol.* 28, 142–149. doi: 10.1016/j.conb.2014.07.005

Pomberger, T., Risueno-Segovia, C., Löschner, J., and Hage, S. R. (2018). Precise motor control enables rapid flexibility in vocal behavior of marmoset monkeys. *Curr. Biol.* 28, 788–794. doi: 10.1016/j.cub.2018.01.070

Putt, S. S., Wijeakumar, S., Franciscus, R. G., and Spencer, J. P. (2017). The functional brain networks that underlie early stone age tool manufacture. *Nat. Hum. Behav.* 1, 1–8. doi: 10.1038/s41562-017-0102

Putt, S. S., Woods, A. D., and Franciscus, R. G. (2014).The role of verbal interaction during experimental bifacial stone tool manufacture. *Lithic Technol.* 39, 96–112. doi: 10.1179/0197726114Z.00000000036

Raghanti, M. A., Edler, M. K., Stephenson, A. R., Munger, E. L., Jacobs, B., Hof, P. R., et al. (2018). A neurochemical hypothesis for the origin of hominids. *Proc. Natl. Acad. Sci. U.S.A.* 115, E1108–E1116. doi: 10.1073/pnas.1719 666115

Rauschecker, J. P. (2012). Ventral and dorsal streams in the evolution of speech and language. *Front. Evol. Neurosci.* 4:7. doi: 10.3389/fnevo.2012.00007

Ridgway, S., Carder, D., Jeffries, M., and Todd, M. (2012). Spontaneous human speech mimicry by a cetacean. *Curr. Biol.* 22, R860–R861. doi: 10.1016/j.cub.2012.08.044

Rilling, J. K. (2014). Comparative primate neurobiology and the evolution of brain language systems. *Curr. Opin. Neurobiol.* 28, 10–14. doi: 10.1016/j.conb.2014.04.002

Rilling, J. K., Glasser, M. F., Jbabdi, S., Andersson, J., and Preuss, T. M. (2012). Continuity, divergence, and the evolution of brain language pathways. *Front. Evol. Neurosci.* 3:11. doi: 10.3389/fnevo.2011.00011

Rilling, J. K., Glasser, M. F., Preuss, T. M., Ma, X., Zhao, T., Hu, X., et al. (2008). The evolution of the arcuate fasciculus revealed with comparative DTI. *Nat. Neurosci.* 11, 426–428. doi: 10.1038/nn2072

Rizzolatti, G., and Arbib, M. A. (1998). Language within our grasp. *Trends Neurosci.* 21, 188–194. doi: 10.1016/S0166-2236(98)01260-0

Rizzolatti, G., Fadiga, L., Gallese, V., and Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. *Cogn. Brain Res.* 3, 131–141. doi: 10.1016/0926-6410(95)00038-0

Romanski, L. M. (2007). Representation and integration of auditory and visual stimuli in the primate ventral lateral prefrontal cortex. *Cereb. Cortex* 17(Suppl. 1), i61–i69. doi: 10.1093/cercor/bhm099

Romanski, L. M., and Goldman-Rakic, P. S. (2002). An auditory domain in primate prefrontal cortex. *Nat. Neurosci.* 5, 15–16. doi: 10.1038/nn781

Sammler, D., Grosbras, M. H., Anwander, A., Bestelmeyer, P. E., and Belin, P. (2015). Dorsal and ventral pathways for prosody. *Curr. Biol.* 25, 3079–3085. doi: 10.1016/j.cub.2015.10.009

Sammler, D., Kotz, S. A., Eckstein, K., Ott, D. V., and Friederici, A. D. (2010). Prosody meets syntax: the role of the corpus callosum. *Brain* 133, 2643–2655. doi: 10.1093/brain/awq231

Saur, D., Kreher, B. W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M. S., et al. (2008). Ventral and dorsal pathways for language. *Proc. Natl. Acad. Sci. U.S.A.* 105, 18035–18040. doi: 10.1073/pnas.0805234105

Schomers, M. R., Garagnani, M., and Pulvermüller, F. (2017). Neurocomputational consequences of evolutionary connectivity changes in Perisylvian language cortex. *J. Neurosci.* 37, 3045–3055. doi: 10.1523/JNEUROSCI.2693-16.2017

Scott, B. H., and Mishkin, M. (2016). Auditory short-term memory in the primate auditory cortex. *Brain Res.* 1640, 264–277. doi: 10.1016/j.brainres.2015.10.048

Scott, B. H., Mishkin, M., and Yin, P. (2012). Monkeys have a limited form of short-term memory in audition. *Proc. Natl. Acad. Sci. U.S.A.* 109, 12237–12241. doi: 10.1073/pnas.1209685109

Seyfarth, R. M., Cheney, D. L., and Marler, P. (1980). Monkey responses to three different alarm calls: evidence of predator classification and semantic communication. *Science* 210, 801–803. doi: 10.1126/science.7433999

Simonyan, K., and Jürgens, U. (2003). Efferent subcortical projections of the laryngeal motorcortex in the rhesus monkey. *Brain Res.* 974, 43–59. doi: 10.1016/S0006-8993(03)02548-4

Skeide, M. A., and Friederici, A. D. (2016). The ontogeny of the cortical language network. *Nat. Rev. Neurosci.* 17, 323–332. doi: 10.1038/nrn.2016.23

Skeide, M. A., Brauer, J., and Friederici, A. D. (2016). Brain functional and structural predictors of language performance. *Cereb. Cortex* 26, 2127–2139. doi: 10.1093/cercor/bhv042

Stoeger, A. S., Mietchen, D., Oh, S., de Silva, S., Herbst, C.T., Kwon, S., et al. (2012). An Asian elephant imitates human speech. *Curr. Biol.* 22, 2144–2148. doi: 10.1016/j.cub.2012.09.022

Stout, D., and Hecht, E. E. (2017). Evolutionary neuroscience of cumulative culture. *Proc. Natl. Acad. Sci. U.S.A.* doi: 10.1073/pnas.1620738114. [Epub ahead of print].

Sugihara, T., Diltz, M. D., Averbeck, B. B., and Romanski, L. M. (2006). Integration of auditory and visual communication information in the primate ventrolateral prefrontal cortex. *J. Neurosci.* 26, 11138–11147. doi: 10.1523/JNEUROSCI.3550-06.2006

Takahashi, D. Y., Fenley, A. R., and Ghazanfar, A. A. (2016). Early development of turn-taking with parents shapes vocal acoustics in infant marmoset monkeys. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 371, 1693. doi: 10.1098/rstb.2015.0370

Takahashi, D. Y., Fenley, A. R., Teramoto, Y., Narayanan, D. Z., Borjon, J. I., Holmes, P., et al. (2015). The developmental dynamics of marmoset monkey vocal production. *Science* 349, 734–738. doi: 10.1126/science.aab1058

Takahashi, D. Y., Narayanan, D. Z., and Ghazanfar, A. A. (2013). Coupled oscillator dynamics of vocal turn-taking in monkeys. *Curr. Biol.* 23, 2162–2168. doi: 10.1016/j.cub.2013.09.005

Takaya, S., Kuperberg, G. R., Liu, H., Greve, D. N., Makris, N., and Stufflebeam, S. M. (2015). Asymmetric projections of the arcuate fasciculus to the temporal cortex underlie lateralized language function in the human brain. *Front. Neuroanat.* 9:119. doi: 10.3389/fnana.2015.00119

Thinh, V. N., Hallam, C., Roos, C., and Hammerschmidt, K. (2011). Concordance between vocal and genetic diversity in crested gibbons. *BMC Evol. Biol.* 11:36. doi: 10.1186/1471-2148-11-36

Tremblay, P., and Dick, A.S. (2016). Broca and Wernicke are dead, or moving past the classic model of language neurobiology. *Brain Lang.* 162, 60–71. doi: 10.1016/j.bandl.2016.08.004

Uomini, N. T., and Meyer, G. F. (2013). Shared brain lateralization patterns in language and Acheulean stone tool production: a functional transcranial Doppler ultrasound study. *PLoS ONE* 8:e72693. doi: 10.1371/journal.pone.0072693

Vias, C., and Dick, A. S. (2017). Cerebellar contributions to language in typical and atypical development: a review. *Dev. Neuropsychol.* 42, 404–421. doi: 10.1080/87565641.2017.1334783

Wilkinson, M., Lim, A. R., Cohen, A. H., Galaburda, A. M., and Takahashi, E. (2017). Detection and growth pattern of arcuate fasciculus from newborn to adult. *Front. Neurosci.* 11:389. doi: 10.3389/fnins.2017.00389

Wilson, B., Marslen-Wilson, W. D., and Petkov, C. I. (2017). Conserved sequence processing in primate frontal cortex. *Trends Neurosci.* 40, 72–82. doi: 10.1016/j.tins.2016.11.004

Yeatman, J. D., Dougherty, R. F., Rykhlevskaia, E., Sherbondy, A. J., Deutsch, G. K., Wandell, B. A., et al. (2011). Anatomical properties of the arcuate fasciculus predict phonological and reading skills in children. *J. Cogn. Neurosci.* 23, 3304–3317. doi: 10.1162/jocn_a_00061

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

OPINION
published: 30 September 2015
doi: 10.3389/fnins.2015.00339

Evolving perceptual biases for antisynchrony: a form of temporal coordination beyond synchrony

Andrea Ravignani[1,2]*

[1] Artificial Intelligence Lab, Vrije Universiteit Brussel, Brussels, Belgium, [2] Sensory and Cognitive Ecology Group, Universität Rostock, Rostock, Germany

Keywords: evolution of communication, group, animal behavior, time perception, social behavior, sexual selection, rhythm, evolution of music

Overview

Many organisms coordinate their group behavior in time. On a short timescale, group vocalizations, movements or visual displays can exhibit temporal interdependence. Synchronous behavior has received significantly more attention than all other forms of animal coordination. Antisynchrony (i.e., perfect alternation) is produced in nature, but only recently perceptual biases toward antisynchrony were independently found in human infants and fiddler crabs. Here, these unrelated experiments are linked and inserted into a broader quantitative framework. Future comparative research should encompass perception of other forms of coordination across species and explanatory levels, toward an integrative neuro-evolutionary framework of temporal coordination.

OPEN ACCESS

Edited by:
Jorge Mpodozis, Universidad de Chile, Chile

Reviewed by:
Yoshimasa Seki, Japan Science and Technology Agency, Japan

***Correspondence:**
Andrea Ravignani, andrea.ravignani@gmail.com

Specialty section:
This article was submitted to Evolutionary Psychology and Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *19 July 2015*
Accepted: *08 September 2015*
Published: *30 September 2015*

Citation:
Ravignani A (2015) Evolving perceptual biases for antisynchrony: a form of temporal coordination beyond synchrony. Front. Neurosci. 9:339. doi: 10.3389/fnins.2015.00339

Synchrony: One among Many Forms of Temporal Interaction

Synchrony, when two or more events take place at exactly the same time, is the most ordered form of temporal coordination (**Figures 1A–D**, top row). Crickets chorus in synchrony, fireflies flash likewise, all with millisecond accuracy (Buck and Buck, 1968; Buck, 1988; Sismondo, 1990; Hartbauer and Römer, 2014). Synchrony does not entail individual intentions to coordinate but often arises as an epiphenomenal by-product of selfish behavior (Greenfield and Roizen, 1993): Individuals want to be noticed. The ecological, behavioral, and neural bases underpinning synchronous behavior have been intensively explored and are increasingly understood (Greenfield et al., 1997; Hartbauer et al., 2005; Fitch, 2015; Iversen et al., 2015).

Yet, synchronous behavior is only one solution to well-coordinated interactions. Many degrees of coordination separate synchrony, like an orchestra in unison, from independent behavior, like several musicians each rehearsing alone (Strogatz and Stewart, 1993; McNeill, 1997). However, perception of all forms of non-synchronous coordination remains mostly unexplored.

Perceptual Biases: What Catches the Eye?

In general, animals show perceptual biases toward particular physical patterns. Here, bias means a predilection of a species' sensory system for particular features, which are perceptually conspicuous to the species. Signallers draw receivers' attention by sending signals; often these signals simply exploit receivers' perceptual biases, rather than advertise good genes and fitness of the signallers (Ryan, 1998). For instance, several animals exhibit colorful fur or plumage, and simultaneously their visual perception is driven toward bright colors. In several animal species, a bias toward red/yellow colors was useful for e.g., finding ripe fruits and was likely also co-opted as a mate selection device.

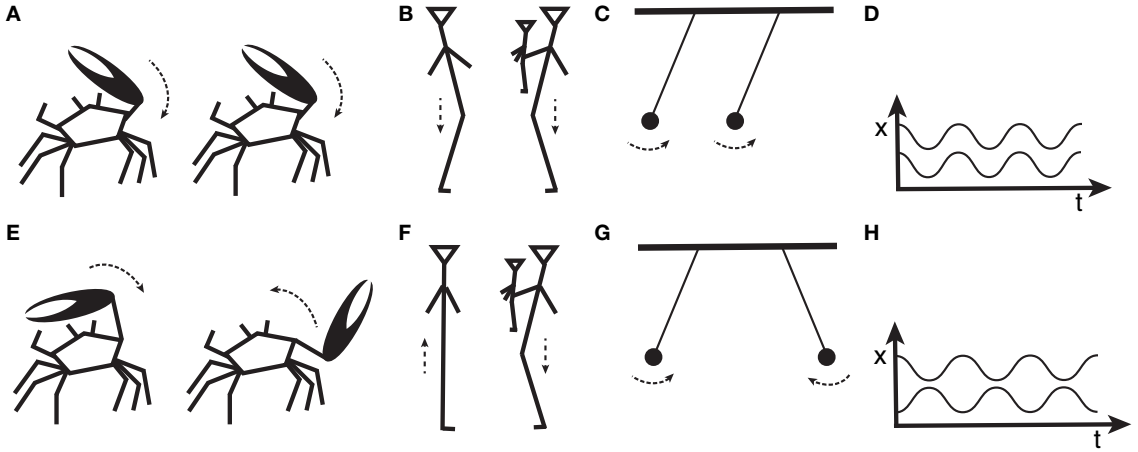


FIGURE 1 | Synthetic representation of synchronous (top row) and antisynchronous (bottom row) coordinated behaviors. Male robotic fiddler crabs wave their larger claw in **(A)** synchrony or **(E)** antisynchrony (Kahn et al., 2014). Similarly, two human adults, one holding an infant, move up, and down to music in **(B)** synchrony, as if each was dancing with her own mirror image or **(F)** antisynchrony, so that one bends her knees while the other stands straight, and vice-versa (Cirelli et al., 2014). Physical oscillators, like pendulums, can resonate at the same frequency; in addition, **(C)** their phase delay can be 0, making them synchronous, or **(G)** half of the oscillatory period, namely π, corresponding to antisynchrony (Strogatz and Stewart, 1993). Events happening in time can be represented graphically by plotting the displacement x–be it the movement of a human leg, a crab's claw or a pendulum–over time t. Plotting time series in this way makes periodic phenomena readily recognizable by their regularly repeating oscillations. In particular, **(D)** synchronous phenomena produce similar sinusoidal waves which can be graphically overlapped, while **(H)** antisynchronous phenomena also produce similar waves, which can however only be overlapped by (phase) shifting one of the sinusoids over time (leftwards or rightwards). Key findings and research efforts to date have been focusing on one particular coordination mode: synchrony (Buck and Buck, 1968; Tuttle and Ryan, 1982; Winfree, 1986; Ermentrout, 1991; Grafe, 1999; Patel et al., 2009; Hasegawa et al., 2011; Merchant et al., 2011; Hattori et al., 2013; Aihara et al., 2014; Fuhrmann et al., 2014; Gamba et al., 2014; Ravignani, 2014; Ravignani et al., 2014a,b; Large and Gray, 2015; Yu and Tomonaga, 2015). However, synchronous behavior is only one outcome of coordinated interactions (Morris et al., 1978; Haimoff, 1986; Grafe, 1999; Bermejo and Omedes, 2000; Yosida and Okanoya, 2005; Mann et al., 2006; Brumm and Slater, 2007; Yosida et al., 2007; Hall, 2009; Ravignani et al., 2013; Aihara et al., 2014; ten Cate, 2014; Hattori et al., 2015); for instance, several species show antiphonal (constant lag) coordination (Sismondo, 1990; Yosida and Okanoya, 2005; Mann et al., 2006; Yosida et al., 2007; Inoue et al., 2013).

A similar logic can be applied, possibly for the first time, to perception of group coordination in the temporal domain[1]. Which sensory biases drive animals toward rhythmic coordination beyond synchrony? Convergent results from child development, animal behavior, and dynamical systems suggest antisynchrony may provide a first answer (**Figures 1E–H**). *Antisynchrony* is the closest alternative to synchrony in physical terms (**Figures 1C–G**). Perceptually, antisynchrony consists in perfect alternation, as in a walking march. In other words, a constant time period separates pairs of antisynchronous movements. Two new experiments in unrelated disciplines simultaneously show that organisms are driven toward the same temporal coordination pattern. Both human infants and crabs exhibit, among others, a perceptual bias toward antisynchrony.

Crabs are Driven toward Antisynchrony

Male fiddler crabs (*Uca mjoebergi*) have one claw larger than the other, which they wave to attract females (Backwell et al., 1998). Each crab finely times its movements depending on the female audience and male competitors. Male fiddler crabs often end up waving in synchrony (**Figure 1A**; Backwell et al., 1998).

Ingenious methodologies and carefully designed experiments have elucidated why temporal interdependence should arise when individual males compete to be noticed by females. Robotic replicas of male crabs were programmed to simulate a number of temporal coordination scenarios, waving in synchrony, antisynchrony, etc. Actual crab females were then tested on their willingness to approach individual robotic crabs, or group of crabs, in different coordination patterns (Reaney et al., 2008). Since individual timing influences perceived attractiveness, females' choices reveal female perceptual biases and preferences for particular temporal patterns. When presented with two groups of male crabs, one waving in synchrony, the other in antisynchrony, females were equally likely to choose between the two groups (Reaney et al., 2008). Female crabs were also tested on their willingness to approach individual robotic crabs *within* a male group. Crucially, the crab waving in antisynchrony with the rest of the group (**Figure 1E**) was one of the favorite among different timing coordination conditions (Kahn et al., 2014).

Movement alternation granted by antisynchrony might be particularly effective to obtain females' attention. Antisynchrony—a previously neglected mode of coordination—was finally shown to be as conspicuous as synchrony in a non-human animal.

[1]This hypothesis of a bias toward the outcome of a group behavior differs from a simple precedence-effect bias toward one individual suggested elsewhere (cf. Reaney et al., 2008; Kahn et al., 2014).

Antisynchrony Triggers Prosociality in Human Infants

Research on human evolution and behavior has profited in the last decades from integration of ethology and human developmental studies (Fitch, 2015; Trainor, 2015). Studying behavioral traits in culturally-naïve infants, and comparing them with similar behaviors in other species, niches and environments, can shed light on human evolution (Hagen and Hammerstein, 2009; Trainor, 2015). It is hence fortunate that cognitive neuroscientists, mutually unbeknown to animal behavior researchers, have also just found biases for antisynchrony in human infants. Temporal movement coordination in human adults has a well-known social role (Cirelli et al., 2014), and temporal coordination and sociality have been usually investigated during synchronous interactions. In particular, perceptual and attentional biases toward movement synchrony are present in humans, and synchronous interactions increase prosocial behaviors, such as cooperation, social cohesion, etc (Hove and Risen, 2009; Miles et al., 2009; Wiltermuth and Heath, 2009; Kirschner and Tomasello, 2010; Manson et al., 2013; Cirelli et al., 2014). When adults are asked to tap together, they soon fall into synchrony or antisynchrony (Knoblich et al., 2011).

Recent experiments in human infants started clarifying the developmental pathways of perceptual biases for coordination, adding antisynchrony to the repertoire. 14-month-old infants were held by an experimenter and exposed to different interpersonal coordination scenarios. In some of those, the experimenter would move the infant up and down in synchrony (**Figure 1B**), antisynchrony (**Figure 1F**) or asynchrony (i.e., random timing) with another adult moving to music. After being bobbed in synchrony and antisynchrony with an adult, infants were more prosocial than after asynchronous movements (Cirelli et al., 2014). In particular, infants exhibited more spontaneous, but not delayed, helping behavior: synchrony and antisynchrony affected early stages of infants' sensory perception, but ceased to influence social behavior as soon as infants exchanged gaze or vocalizations with an adult. This suggests that Cirelli et al.'s experimental setup (i) tapped into early, possibly evolutionary ancient neuroethological traits (Trainor, 2015) dating to our last common ancestor with great apes, or earlier (Fitch, 2009; Giacoma et al., 2010; Hagmann and Cook, 2010; Dunbar, 2012; Gamba et al., 2014; Dufour et al., 2015; Large and Gray, 2015; Yu and Tomonaga, 2015), hence their results could help uncover the phylogenetic bases of rhythm; (ii) engaged human participants' subcortical brain structures [such as basal ganglia, usually involved in perception of rhythmic patterns (Grahn and Brett, 2007; Kotz and Schmidt-Kassow, 2015)], again suggesting that preferences for (anti)synchrony are likely to be found in other animals due to common ancestry.

Human Temporal Coordination: Evolution and Functions

In human evolutionary history, refined temporal coordination and perception abilities might predate the origins of music and speech (Bryant, 2014; Ravignani et al., 2014c). Finely coordinated dance and music might have initially arisen as a social device, possibly as a signal of group cohesion (Merker, 2000; Hagen and Bryant, 2003; Merker et al., 2009; Dunbar, 2012). Now, every signaling system relies on a perceptual repertoire, which can be exploited for communication: biases toward particular temporal coordination patterns, like synchrony and antisynchrony, could have offered such fertile perceptual substrate for a joint group signaling system. The hypothesis that (anti)synchrony mediated group coordination and music origins is supported by another "evolutionary leftover" found in the auditory domain. Modern humans prefer syncopated music (Fitch and Rosenfeld, 2007; Keller and Schubert, 2011), which also provides a sense of groove (urge to move rhythmically, Janata et al., 2012). Crucially, syncopated rhythms in music often correspond to musical notes in antisynchrony with the underlying beat.

A Common Perceptual Bias for Antisynchrony?

Infants and fiddler crabs are driven toward the same form of mild asynchrony. A basic perceptual bias for a simple coordination mode—antisynchrony—might have been a precursor for behaviors as different as prosociality and mate selection. (This would be analogous to a single physical trait exapted by two species for different usages, e.g., humans walk on legs, harbor seals swim with hind-flippers, and both limb types evolved from the back legs of our quadruped ancestor). Why would specifically antisynchrony be exapted, and not other coordination modes? Antisynchronous movements reunite two conditions: they follow periods of no waving and, by definition, are uncluttered by other synchronous movements (Kahn et al., 2014).

Once this qualitative argument is formulated mathematically, it can be generalized to any number of oscillators and equals the problem of evenly spacing interdependent onsets over time. Antisynchrony is its natural solution for two signallers. Among all possible phase relationships between oscillators, antisynchronous movements are *minimally* cluttered by others and occupy the sweet spot in time where no other animal has signaled, or will signal, for a whole *half period* (i.e., their onsets are evenly distributed and spaced in time, **Figure 1H**).

Neural Mechanisms Underlying Signal Production, Perception, and Biases need not Coincide

The neural mechanisms for *performing* and *perceiving* coordinated movements in humans and crabs are likely to differ (Hulse et al., 1984; Hulse and Kline, 1993; Harley et al., 2002; Hagmann and Cook, 2010; Hasegawa et al., 2011; Sztarker and Tomsic, 2011). Perception and production of rhythmic patterns seem to correlate with vocal learning across species (Patel, 2006, 2008; Patel et al., 2009; Schachner, 2010). Auditory and motor planning regions of the human cortex are linked more strongly than in many other species via dorsal auditory pathway connections (Patel and Iversen, 2014). This would

explain the extreme flexibility some vocal learning mammals have in imitating new sounds by readily mapping perceived vocalizations into orofacial movements.

The neural bases of processing rhythmic information in crabs should be close to other arthropods. Common ancestry would suggest that crabs, like crickets or fireflies, use an 'inflexible' *phase-resetting* mechanism to time their movements (like turning a metronome off and on again). However, crabs appear more flexible than their insect relatives, decreasing the wave duration and between-wave pause the closer a female crab approaches (How et al., 2008). This offers initial support for the hypothesis that crabs might have a human-like *frequency modulation* mechanism (speeding up or slowing down, like a DJ mixing songs with different tempos). This hypothesis can be tested in fiddler crabs by varying the stimulus rate and adapting a suite of well-developed experimental paradigms (Repp, 2005; Repp and Su, 2013).

Several animals show antiphonal interactions (Ravignani et al., 2014b), which at least in a frog species (*Hyla japonica*) seem to reach the perfect alternation of antisynchronous calling (Aihara et al., 2014). However, group production of antisynchronous signals does not imply its perception. In turn, perceptual biases for a coordination pattern can only, although need not, emerge if a particular species already perceives that pattern.

Future Experiments Across Species: Dynamical Systems as Roadmap to Test the Neuropsychology and Genetics of Perceived Coordination

Perceptual antisynchrony is the first step to uncover the perception of coordination patterns across species. While systematic classification of interdependent temporal signaling in the animal kingdom is ongoing (Ravignani et al., 2014b), no common measure of (perceived) coordination complexity exists yet. Such measure would allow ranking different coordination patterns (synchrony, randomness, non-synchronous interdependence, etc.) along a neurobiological, perceptual dimension. The species tested until now seem to prefer synchrony, antisynchrony or both. Similarly, oscillators in synchrony and antisynchrony, although corresponding to the seemingly opposite phenomena of unison and alternation, are extremely close to each other in physical terms (**Figures 1C,G**). *Physical* measures of coordination complexity, as in dynamical systems (Winfree, 1986; Strogatz and Stewart, 1993; Strogatz, 2000; Large, 2008), might provide a valuable first approximation to *perceived* coordination.

Future behavioral research should test perception of different coordination patterns across species. Building on behavioral results, the long term goal will be to uncover the neuro-(epi)genetics (Lachmann and Jablonka, 1996; Petkov and Jarvis, 2012; Bronfman et al., 2014; Wilkins et al., 2014; Jablonka and Lamb, 2015) of temporal coordination. Recent evidence from musicians provides a first molecular and genetic link between joint coordinated actions and its perception, possibly transcending individual species. Researchers studied the genes transcribed after music performance (Kanduri et al., 2015a) and listening (Kanduri et al., 2015b), finding striking similarities with genes involved in song perception and production in songbirds. This suggests that some ancestral biological processes related to auditory-motor behavior, now crucial for song and speech, were preserved during 300 million years of independent evolutionary history (Kanduri et al., 2015a).[2] Comparative research will enable mapping phylogenetic relations between species to the physical space of coordination patterns they perceive, hence unraveling the evolutionary history of those traits by homology or analogy (Tinbergen, 1963; Calvin, 1983; Ravignani et al., 2014a,b; Faunes et al., 2015).

Funding

The author was supported by FWO grant V439315N (to Andrea Ravignani), and European Research Council grants 283435 ABACUS (to Bart de Boer) and 230604 SOMACCA (to W. Tecumseh Fitch).

Acknowledgments

I sincerely thank Allison Binley, Bart de Boer, Elvita Eglîte, Piera Filippi, Tamara Heinrich, Miriam Kirsch, Eoin O'Sullivan, Silvia Prislei, Elena Ravignani, Ruth Sonnweber, and Bill Thompson for invaluable comments on earlier versions of this paper. I am grateful to the editor Jorge Mpodozis, Yoshimasa Seki, and two anonymous referees for their advice and support during the review process.

[2] Perhaps few genetic commonalities underlie biases toward (anti)synchrony across species. Pending evidence from additional species, an antisynchrony bias in both humans and crabs is most parsimoniously (minimum number of gains and losses in a phylogenetic tree, cf. Petkov and Jarvis, 2012) explained by analogy.

References

Aihara, I., Mizumoto, T., Otsuka, T., Awano, H., Nagira, K., Okuno, H. G., et al. (2014). Spatio-temporal dynamics in collective frog choruses examined by mathematical modeling and field observations. *Sci. Rep.* 4:3891. doi: 10.1038/srep03891

Backwell, P., Jennions, M., Passmore, N., and Christy, J. (1998). Synchronized courtship in fiddler crabs. *Nature* 391, 31–32. doi: 10.1038/34076

Bermejo, M., and Omedes, A. (2000). Preliminary vocal repertoire and vocal communication of wild bonobos (*Pan paniscus*) at Lilungu (Democratic Republic of Congo). *Folia Primatologica* 70, 328–357. doi: 10.1159/000021717

Bronfman, Z. Z., Ginsburg, S., and Jablonka, E. (2014). Shaping the learning curve: epigenetic dynamics in neural plasticity. *Front. Integr. Neurosci.* 8:55. doi: 10.3389/fnint.2014.00055

Brumm, H., and Slater, P. (2007). Animal communication: timing counts. *Curr. Biol.* 17, R521–R523. doi: 10.1016/j.cub.2007.04.053

Bryant, G. A. (2014). The evolution of coordinated vocalizations before language. *Behav. Brain Sci.* 37, 549–550. doi: 10.1017/S0140525X1300397X

Buck, J., and Buck, E. (1968). Mechanism of Rhythmic Synchronous Flashing of Fireflies Fireflies of Southeast Asia may use anticipatory time-measuring in synchronizing their flashing. *Science* 159, 1319–1327. doi: 10.1126/science.159.3821.1319

Buck, J. (1988). Synchronous rhythmic flashing in fireflies. II. *Q. Rev. Biol.* 63, 265–287. doi: 10.1086/415929

Calvin, W. H. (1983). A stone's throw and its launch window: timing precision and its implications for language and hominid brains. *J. Theor. Biol.* 104, 121–135. doi: 10.1016/0022-5193(83)90405-8

Cirelli, L. K., Einarson, K. M., and Trainor, L. J. (2014). Interpersonal synchrony increases prosocial behavior in infants. *Dev. Sci.* 17, 1003–1011. doi: 10.1111/desc.12193

Dufour, V., Poulin, N., Curé, C., and Sterck, E. H. (2015). Chimpanzee drumming: a spontaneous performance with characteristics of human musical drumming. *Sci. Rep.* 5:11320. doi: 10.1038/srep11320

Dunbar, R. (2012). "On the evolutionary function of song and dance," in *Music Language, and Human Evolution*, ed N. Bannan (Oxford, UK: Oxford University press), 201–214.

Ermentrout, B. (1991). An adaptive model for synchrony in the firefly *Pteroptyx malaccae*. *J. Math. Biol.* 29, 571–585. doi: 10.1007/BF00164052

Faunes, M., Francisco Botelho, J., Ahumada Galleguillos, P., and Mpodozis, J. (2015). On the hodological criterion for homology. *Front. Neurosci.* 9:223. doi: 10.3389/fnins.2015.00223

Fitch, W. T., and Rosenfeld, A. J. (2007). Perception and production of syncopated rhythms. *Music Percept.* 25, 43–58. doi: 10.1525/mp.2007.25.1.43

Fitch, W. T. (2009). "The biology and evolution of rhythm: unraveling a paradox," in *Language and Music as Cognitive Systems*, eds P. Rebuschat, M. Rohrmeier, J. A. Hawkins, and I. Cross (Oxford, UK: Oxford University Press), 73–95.

Fitch, W. T. (2015). Four principles of bio-musicology. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 370:20140091. doi: 10.1098/rstb.2014.0091

Fuhrmann, D., Ravignani, A., Marshall-Pescini, S., and Whiten, A. (2014). Synchrony and motor mimicking in chimpanzee observational learning. *Sci. Rep.* 4:5283. doi: 10.1038/srep05283

Gamba, M., Torti, V., Bonadonna, G., Guzzo, G., and Giacoma, C. (2014). "Overlapping and synchronization in the song of the Indris (Indri indri)," in *The Evolution of Language: Proceedings of the 10th international conference*, eds S. R. Ea Cartmill, H. Lyn, and H. Cornish (Singapore: World Scientific Press), 90–97.

Giacoma, C., Sorrentino, V., Rabarivola, C., and Gamba, M. (2010). Sex differences in the song of Indri indri. *Int. J. Primatol.* 31, 539–551. doi: 10.1007/s10764-010-9412-8

Grafe, T. U. (1999). A function of synchronous chorusing and a novel female preference shift in an anuran. *Proc. R. Soc. Lond. B Biol. Sci.* 266, 2331–2336. doi: 10.1098/rspb.1999.0927

Grahn, J. A., and Brett, M. (2007). Rhythm and beat perception in motor areas of the brain. *J. Cogn. Neurosci.* 19, 893–906. doi: 10.1162/jocn.2007.19.5.893

Greenfield, M. D., and Roizen, I. (1993). Katydid synchronous chorusing is an evolutionarily stable outcome of female choice. *Nature* 364, 618–620. doi: 10.1038/364618a0

Greenfield, M. D., Tourtellot, M. K., and Snedden, W. A. (1997). Precedence effects and the evolution of chorusing. *Proc. R. Soc. Lond. B Biol. Sci.* 264, 1355–1361. doi: 10.1098/rspb.1997.0188

Hagen, E. H., and Bryant, G. A. (2003). Music and dance as a coalition signaling system. *Hum. Nat.* 14, 21–51. doi: 10.1007/s12110-003-1015-z

Hagen, E. H., and Hammerstein, P. (2009). Did Neanderthals and other early humans sing? Seeking the biological roots of music in the territorial advertisements of primates, lions, hyenas, and wolves. *Musicae Sci.* 13, 291–320. doi: 10.1177/1029864909013002131

Hagmann, C. E., and Cook, R. G. (2010). Testing meter, rhythm, and tempo discriminations in pigeons. *Behav. Process.* 85, 99–110. doi: 10.1016/j.beproc.2010.06.015

Haimoff, E. H. (1986). Convergence in the duetting of monogamous Old World primates. *J. Hum. Evol.* 15, 51–59. doi: 10.1016/S0047-2484(86)80065-3

Hall, M. L. (2009). A review of vocal duetting in birds. *Adv. Study Behav.* 40, 67–121. doi: 10.1016/S0065-3454(09)40003-2

Harley, H., Odell, K., Outnam, E., Goonen, C., and Delong, C. M. (2002). "Dolphins perceive rhythm: a belated ode to Stewart Hulse," in *9th International Conference on Comparative Cognition* (Melbourne Beach, FL).

Hartbauer, M., Kratzer, S., Steiner, K., and Römer, H. (2005). Mechanisms for synchrony and alternation in song interactions of the bushcricket Mecopoda elongata (Tettigoniidae: Orthoptera). *J. Comp. Physiol. A* 191, 175–188. doi: 10.1007/s00359-004-0586-4

Hartbauer, M., and Römer, H. (2014). From microseconds to seconds and minutes-time computation in insect hearing. *Front. Physiol.* 5:138. doi: 10.3389/fphys.2014.00138

Hasegawa, A., Okanoya, K., Hasegawa, T., and Seki, Y. (2011). Rhythmic synchronization tapping to an audio-visual metronome in budgerigars. *Sci. Rep.* 1:120. doi: 10.1038/srep00120

Hattori, Y., Tomonaga, M., and Matsuzawa, T. (2013). Spontaneous synchronized tapping to an auditory rhythm in a chimpanzee. *Sci. Rep.* 3:1566. doi: 10.1038/srep01566

Hattori, Y., Tomonaga, M., and Matsuzawa, T. (2015). Distractor effect of auditory rhythms on self-paced tapping in Chimpanzees and humans. *PLoS ONE* 10:e0130682. doi: 10.1371/journal.pone.0130682

Hove, M. J., and Risen, J. L. (2009). It's all in the timing: interpersonal synchrony increases affiliation. *Soc. Cogn.* 27, 949–960. doi: 10.1521/soco.2009.27.6.949

How, M. J., Hemmi, J. M., Zeil, J., and Peters, R. (2008). Claw waving display changes with receiver distance in fiddler crabs, Uca perplexa. *Anim. Behav.* 75, 1015–1022. doi: 10.1016/j.anbehav.2007.09.004

Hulse, S. H., Humpal, J., and Cynx, J. (1984). Processing of rhythmic sound structures by Birdsa. *Ann. N. Y. Acad. Sci.* 423, 407–419. doi: 10.1111/j.1749-6632.1984.tb23449.x

Hulse, S. H., and Kline, C. L. (1993). The perception of time relations in auditory tempo discrimination. *Anim. Learn. Behav.* 21, 281–288. doi: 10.3758/BF03197992

Inoue, Y., Sinun, W., Yosida, S., and Okanoya, K. (2013). Intergroup and intragroup antiphonal songs in wild male MuellerÄôs gibbons (Hylobates muelleri). *Interact. Stud.* 14, 24–43. doi: 10.1075/is.14.1.03ino

Iversen, J. R., Patel, A. D., Nicodemus, B., and Emmorey, K. (2015). Synchronization to auditory and visual rhythms in hearing and deaf individuals. *Cognition* 134, 232–244. doi: 10.1016/j.cognition.2014.10.018

Jablonka, E., and Lamb, M. J. (2015). The inheritance of acquired epigenetic variations. *Int. J. Epidemiol.* dyv020. doi: 10.1093/ije/dyv020. [reprinted with permission from Jablonka, E., and Lamb, M. J. (1989). The Inheritance of acquired epigenetic variations. J. theor. Bioi. 139:69–83].

Janata, P., Tomic, S. T., and Haberman, J. M. (2012). Sensorimotor coupling in music and the psychology of the groove. *J. Exp. Psychol. Gen.* 141, 54. doi: 10.1037/a0024208

Kahn, A. T., Holman, L., and Backwell, P. R. (2014). Female preferences for timing in a fiddler crab with synchronous courtship waving displays. *Anim. Behav.* 98, 35–39. doi: 10.1016/j.anbehav.2014.09.028

Kanduri, C., Kuusi, T., Ahvenainen, M., Philips, A. K., Lähdesmäki, H., and Järvelä, I. (2015a). The effect of music performance on the transcriptome of professional musicians. *Sci. Rep.* 5:9506. doi: 10.1038/srep09506

Kanduri, C., Raijas, P., Ahvenainen, M., Philips, A. K., Ukkola-Vuoti, L., Lähdesmäki, H., et al. (2015b). The effect of listening to music on human transcriptome. *Peer J.* 3:e830. doi: 10.7717/peerj.830

Keller, P. E., and Schubert, E. (2011). Cognitive and affective judgements of syncopated musical themes. *Adv. Cogn. Psychol.* 7, 142–156. doi: 10.2478/v10053-008-0094-0

Kirschner, S., and Tomasello, M. (2010). Joint music making promotes prosocial behavior in 4-year-old children. *Evol. Hum. Behav.* 31, 354–364. doi: 10.1016/j.evolhumbehav.2010.04.004

Knoblich, G., Butterfill, S., and Sebanz, N. (2011). 3 Psychological research on joint action: theory and data. *Psychol. Learn. Motiv. Adv. Res. Theory* 54, 59. doi: 10.1016/B978-0-12-385527-5.00003-6

Kotz, S. A., and Schmidt-Kassow, M. (2015). Basal ganglia contribution to rule expectancy and temporal predictability in speech. *Cortex* 68, 48–60. doi: 10.1016/j.cortex.2015.02.021

Lachmann, M., and Jablonka, E. (1996). The inheritance of phenotypes: an adaptation to fluctuating environments. *J. Theor. Biol.* 181, 1–9. doi: 10.1006/jtbi.1996.0109

Large, E. W., and Gray, P. M. (2015). Spontaneous tempo and rhythmic entrainment in a Bonobo (*Pan Paniscus*). *J. Comp. Psychol.* doi: 10.1037/com0000011. [Epub ahead of print].

Large, E. W. (2008). Resonating to musical rhythm: theory and experiment. *Psychol. Time* 189–232. doi: 10.1016/B978-0-08046-977-5.00006-5

Mann, N. I., Dingess, K. A., and Slater, P. (2006). Antiphonal four-part synchronized chorusing in a Neotropical wren. *Biol. Lett.* 2, 1–4. doi: 10.1098/rsbl.2005.0373

Manson, J. H., Bryant, G. A., Gervais, M. M., and Kline, M. A. (2013). Convergence of speech rate in conversation predicts cooperation. *Evol. Hum. Behav.* 34, 419–426. doi: 10.1016/j.evolhumbehav.2013.08.001

McNeill, W. H. (1997). *Keeping Together in Time.* Cambridge, MA: Harvard University Press.

Merchant, H., Zarco, W., Pérez, O., Prado, L., and Bartolo, R. N. (2011). Measuring time with different neural chronometers during a synchronization-continuation task. *Proc. Natl. Acad. Sci. U.S.A.* 108, 19784–19789. doi: 10.1073/pnas.1112933108

Merker, B., Madison, G. S., and Eckerdal, P. (2009). On the role and origin of isochrony in human rhythmic entrainment. *Cortex* 45, 4–17. doi: 10.1016/j.cortex.2008.06.011

Merker, B. (2000). Synchronous chorusing and the origins of music. *Musicae Sci.* 3, 59–73. doi: 10.1177/10298649000030S105

Miles, L. K., Nind, L. K., and Macrae, C. N. (2009). The rhythm of rapport: Interpersonal synchrony and social perception. *J. Exp. Soc. Psychol.* 45, 585–589. doi: 10.1016/j.jesp.2009.02.002

Morris, G. K., Kerr, G. E., and Fullard, J. H. (1978). Phonotactic preferences of female meadow katydids (Orthoptera: Tettigoniidae: *Conocephalus nigropleurum*). *Can. J. Zool.* 56, 1479–1487. doi: 10.1139/z78-205

Patel, A. D., and Iversen, J. R. (2014). The evolutionary neuroscience of musical beat perception: the Action Simulation for Auditory Prediction (ASAP) hypothesis. *Front. Syst. Neurosci.* 8:57. doi: 10.3389/fnsys.2014.00057

Patel, A. D., Iversen, J. R., Bregman, M. R., and Schulz, I. (2009). Experimental evidence for synchronization to a musical beat in a nonhuman animal. *Curr. Biol.* 19, 827–830. doi: 10.1016/j.cub.2009.03.038

Patel, A. D. (2006). Musical rhythm, linguistic rhythm, and human evolution. *Music Percept.* 24, 99–104. doi: 10.1525/mp.2006.24.1.99

Patel, A. D. (2008). *Music, Language, and the Brain.* New York, NY: Oxford University Press.

Petkov, C. I., and Jarvis, E. D. (2012). Birds, primates, and spoken language origins: behavioral phenotypes and neurobiological substrates. *Front. Evol. Neurosci.* 4:12. doi: 10.3389/fnevo.2012.00012

Ravignani, A., Bowling, D., and Kirby, S. (2014a). "The psychology of biological clocks: a new framework for the evolution of rhythm," in *The Evolution of Language: Proceedings of the 10th International Conference,* eds S. R. Ea Cartmill, H. Lyn, and H. Cornish (Singapore: World Scientific Press), 262–269.

Ravignani, A., Bowling, D. L., and Fitch, W. T. (2014b). Chorusing, synchrony and the evolutionary functions of rhythm. *Front. Psychol.* 5:1118. doi: 10.3389/fpsyg.2014.01118

Ravignani, A., Martins, M., and Fitch, W. (2014c). Vocal learning, prosody, and basal ganglia: don't underestimate their complexity. *Behav. Brain Sci.* 37, 570–571. doi: 10.1017/S0140525X13004184

Ravignani, A., Olivera, V. M., Gingras, B., Hofer, R., Hernández, C. R., Sonnweber, R.-S., et al. (2013). Primate Drum Kit: a system for studying acoustic pattern production by non-human primates using acceleration and strain sensors. *Sensors* 13, 9790–9820. doi: 10.3390/s130809790

Ravignani, A. (2014). Chronometry for the chorusing herd: Hamilton's legacy on context-dependent acoustic signalling-a comment on Herbers (2013). *Biol. Lett.* 10:20131018. doi: 10.1098/rsbl.2013.1018

Reaney, L. T., Sims, R. A., Sims, S. W., Jennions, M. D., and Backwell, P. R. (2008). Experiments with robots explain synchronized courtship in fiddler crabs. *Curr. Biol.* 18, R62–R63. doi: 10.1016/j.cub.2007.11.047

Repp, B. H., and Su, Y.-H. (2013). Sensorimotor synchronization: A review of recent research (2006-2012). *Psychon. Bull. Rev.* 20, 403–452. doi: 10.3758/s13423-012-0371-2

Repp, B. H. (2005). Sensorimotor synchronization: a review of the tapping literature. *Psychon. Bull. Rev.* 12, 969–992. doi: 10.3758/BF03206433

Ryan, M. J. (1998). Sexual selection, receiver biases, and the evolution of sex differences. *Science* 281, 1999–2003. doi: 10.1126/science.281.5385.1999

Schachner, A. (2010). Auditory-motor entrainment in vocal mimicking species: Additional ontogenetic and phylogenetic factors. *Commun. Integr. Biol.* 3, 290–293. doi: 10.4161/cib.3.3.11708

Sismondo, E. (1990). Synchronous, alternating, and phase-locked stridulation by a tropical katydid. *Science* 249, 55–58. doi: 10.1126/science.249.4964.55

Strogatz, S. H., and Stewart, I. (1993). Coupled oscillators and biological synchronization. *Sci. Am.* 269, 102–109. doi: 10.1038/scientificamerican1293-102

Strogatz, S. H. (2000). From Kuramoto to Crawford: exploring the onset of synchronization in populations of coupled oscillators. *Physica D.* 143, 1–20. doi: 10.1016/S0167-2789(00)00094-4

Sztarker, J., and Tomsic, D. (2011). Brain modularity in arthropods: individual neurons that support "what" but not "where" memories. *J. Neurosci.* 31, 8175–8180. doi: 10.1523/JNEUROSCI.6029-10.2011

ten Cate, C. (2014). On the phonetic and syntactic processing abilities of birds: from songs to speech and artificial grammars. *Curr. Opin. Neurobiol.* 28, 157–164. doi: 10.1016/j.conb.2014.07.019

Tinbergen, N. (1963). On aims and methods of ethology. *Zeitschrift für Tierpsychologie* 20, 410–433. doi: 10.1111/j.1439-0310.1963.tb01161.x

Trainor, L. J. (2015). The origins of music in auditory scene analysis and the roles of evolution and culture in musical creation. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 370:20140089. doi: 10.1098/rstb.2014.0089

Tuttle, M. D., and Ryan, M. J. (1982). The role of synchronized calling, ambient light, and ambient noise, in anti-bat-predator behavior of a treefrog. *Behav. Ecol. Sociobiol.* 11, 125–131. doi: 10.1007/BF00300101

Wilkins, A. S., Wrangham, R. W., and Fitch, W. T. (2014). The "domestication syndrome" in mammals: a unified explanation based on neural crest cell behavior and genetics. *Genetics* 197, 795–808. doi: 10.1534/genetics.114.165423

Wiltermuth, S. S., and Heath, C. (2009). Synchrony and cooperation. *Psychol. Sci.* 20, 1–5. doi: 10.1111/j.1467-9280.2008.02253.x

Winfree, A. T. (1986). *Timing of Biological Clocks.* Oxford, UK: Scientific American Library.

Yosida, S., Kobayasi, K. I., Ikebuchi, M., Ozaki, R., and Okanoya, K. (2007). Antiphonal Vocalization of a Subterranean Rodent, the Naked Mole-Rat (Heterocephalus glaber). *Ethology* 113, 703–710. doi: 10.1111/j.1439-0310.2007.01371.x

Yosida, S., and Okanoya, K. (2005). Animal cognition evolution of turn-taking: a bio-cognitive perspective. *Cogn. Stud.* 12, 153–165. doi: 10.11225/jcss.12.153

Yu, L., and Tomonaga, M. (2015). Interactional synchrony in chimpanzees: examination through a finger-tapping experiment. *Sci. Rep.* 5:10218. doi: 10.1038/srep10218

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

OPINION
published: 06 December 2016
doi: 10.3389/fpsyg.2016.01880

I Can't Get No (Boolean) Satisfaction: A Reply to Barrett et al. (2015)

Robert King *

School of Applied Psychology, University College Cork, Cork, Ireland

Keywords: evolutionary psychology, extended mind, cognition, embodied cognition, artificial intelligence

Sometimes history can be philosophically interesting. Barrett (2011) and colleagues (e.g., Barrett et al., 2014, 2015) are to be congratulated on widening the scope of our understanding of animal cognition to include its ecological elements. However, in their eagerness to overturn a narrow model of computation, she and her colleagues have glossed over some rather interesting and salient historical facts. This is poignant, as these facts strengthen their case, and sharpen the focus on the more complete picture of ethologically valid cognition that they are drawing.

The key figure missing from the usual historical narrative is George Boole, whose bi-centenary has just passed and (it just so happens) is the luminary whose soon-to-be-restored home is visible from the office where I type this, in the University he led, and on the machine that his insights made possible.

Barrett (2011) wants to draw a distinction between computation—in a narrow sense–abstracted from any particular setting, and the highly embodied—especially ecologically rooted–cognition that she sees in the animals she studies.

In support of this distinction, she cites Searle's (1990) claim that, as a matter of history, humans tend to use their most impressive piece of technology as a mental metaphor. As exemplars, the ancient Greeks used models of torque-powered siege devices, de La Mettrie's (1960) L'Homme Machine used images of clockwork brains, Freud's libidinous mind was powered by hydraulic instincts, and so on (see Daugman, 2001 for a more extended discussion).

But, as an important historical fact the order of technology-then-metaphor is the other way round in respect of the computational model. Thinking about thinking—specifically Boole's thinking about thinking–came long before the technology did. The technology grew out of it. Thus, it's less true to say that computers are a metaphor for thinking, than that thinking is a metaphor for computation.

One important difference that modern computers have from the "technology as metaphor" pattern is that in none of the other cases have advances been made in the technology as a result of the comparison. Fountains, hydraulics, and clockwork did not become more sophisticated by reflecting on their mind-like properties. On the other hand, artificial intelligence has advanced considerably—to the point where it might be said, without hyperbole, that AI is in many cases the proof that psychology as a science is advancing. When we can formalize an information processing subsystem we can mechanize it. The fact is that we now live in a world where cars drive themselves, airplanes land themselves, and face recognition software finally works.

Deep Mind is living (!) proof that that the Rescorla and Wagner (1972) model of conditional learning works and this is not a unique example (Van Hasselt et al., 2015). The human mind isn't a computer (Searle is right about this) but it does have thousands of computable functions and we are making progress in understanding them. Will there be anything left over when we have solved all these so-called easy problems of Chalmers (1996)? It is too early to say. However, one thing that won't be left over is the ecology. Barrett et al. (2015) have seen to that, by drawing attention to the fact that said functions will be incomplete unless put in ecological (e.g., locally adaptive) contexts. And that's progress, but it is still functionalist progress. Indeed—it's a justly celebrated advance on the Gibsonian programme of embodied functional analysis of cognition. But—it is not

OPEN ACCESS

Edited by:
Jorge Mpodozis, University of Chile, Chile

Reviewed by:
Louise Barrett, University of Lethbridge, Canada

***Correspondence:**
Robert King
r.king@ucc.ie

Specialty section:
This article was submitted to Evolutionary Psychology and Neuroscience, a section of the journal Frontiers in Psychology

Received: *12 August 2016*
Accepted: *15 November 2016*
Published: *06 December 2016*

Citation:
King R (2016) I Can't Get No (Boolean) Satisfaction: A Reply to Barrett et al. (2015). Front. Psychol. 7:1880. doi: 10.3389/fpsyg.2016.01880

less functionalist for all that. It turns out that the details of being an adapted organism (functioning in its ecology) cannot be fully abstracted into discrete disembodied modules fully specifiable in terms of brains alone. This might lead some to prematurely think that functionalism has met its nadir, but this would be a mistake. Before I get to why this is I need to say a few things about the Boolean programme that underlies the functionalist revolution in cognitive science.

For an exhaustive exegesis of Boole's work here the authority is (Corcoran, 2003), but the key ideas are quite accessible. Boole's basic insight receives its fullest expression in The Laws of Thought (Boole, 1854) and this is an attempt to draw in all human cognition (it was never about just mathematics) together in terms of the deep underlying logical structure in the most abstract form possible, while still being recognizable at a syntactic level—this level being instantiated (in computers) in terms of logic gates. Formalizing cognition was itself the process which allowed physical computers to be eventually possible.

The major later figures in this development are well known. They include (but are not limited to) Claude Shannon, whose 1947 master's thesis ushered in modern information theory, through Alan Turing whose 1950 paper offered a principled way to instantiate a machine that could compute any computable function (Turing, 1950). John von Neumann's complex proof of how any machine is really a representation of a function (and might thereby replicate itself) was also an important landmark, in von Neumann and Burks (1966). Although all of these papers had important practical outcomes and were (non-accidentally) made by people with engineering connections, they were not "how to build" papers. They were concerned with the formal ways to represent cognition at the most basic level appreciable by human beings. Note that this is not the same as saying that this is the only level they exist at. Those formalizations resulted in physical objects—such as the one I am typing this on—but the causal arrow was not from object to concept. Computers (such as the ones used to crack the Enigma codes) existed by the time of Shannon, Turing, and others but the foundational functionalist work had been done a century before by Boole. Thus, it is strictly illegitimate to say that functionalism, as a strategy for decomposing thought, relies on the computer metaphor. The functionalism came first.

So much for history. Are there independent reasons for thinking that the functionalist programme is not to be lightly set aside? Indeed there are, but here I will only mention a few relevant to Barrett et al. (2015) general programme, which I should stress, are not things that they necessarily deny.

It's commonly asserted that the computational metaphor is about the formal manipulation of symbols (Searle, 1990). But this is a half-truth. At one level, a level that makes semantic sense to a human observer, computers manipulate symbols. But mainly what they do is turn logic gates on and off really fast. And no human observer would be able to make any sense of that at the speeds that it occurs in a modern computer. Of course, if you delve deeper still what we have in the computer is bits of information, and witnessing that wouldn't convey anything much that an unaided human observer could make meaningful. Indeed, the (physical) computer is itself the aid. Boole's key insight was to analyse the logic of human cognition at the mid-level and realize that this level could be formalized. And once something can be formalized it can be mechanized. And the proof that he was right is the tasty pudding of modern computing—which undeniably works, or you would not be reading this.

Does a modern desktop computer (or any computer for that matter) replicate human consciousness? Of course it doesn't. But the formalization of human cognition is a different matter—the computer comes along almost as a by-product of the attempt to do that (albeit a by-product that demonstrates that we must be on to something).

It might be objected that humans do not naturally think in terms of logic gates. And this is true, but hardly to the point. We are typically unconscious of the underlying computational structure of things that come naturally to us. Most of us are unconscious of the grammar of our native tongues unless it is formally taught to us, and it is entirely unnecessary to learn the formal grammar of a language to be able to converse in it. Nevertheless, the formal grammar lays bare the structure of that language.

A follow-up objection might be that, while it is admitted that Boole laid bare the formal elements of some aspects of human thought, there are others left untouched. This may well be true and if it is true then the attempt to build upon his insights with formal instantiations of computation into physical systems that replicate human thought will be forever doomed. Once again—it is too early to tell.

One further common mistake is to note that humans aren't conscious of these sorts of processes. Cognition is not consciousness. Moravec (2000) drew insightful attention to precisely this fact. He noted that the tasks that required very smart humans to perform (e.g., diagnose disease, fly airplanes, play chess) were comparatively trivial to automate (incidentally—this doesn't imply that the automated version completely captures the path of human cognition to achieving them). At the same time, it proved very hard to automate things that to humans were trivial, such as climbing stairs and recognizing faces. The solution to this paradox is that evolutionarily ancient processes do not need to draw on novel conscious elements. But—and this is the crucial point—they are nonetheless cognitive functions for all that.

Computational modeling is rooted in the realization that all observations reveal detectable differences. These are information. If a set of these can be meaningfully grouped into a system then a change is a state change, and any regularities in such changes describe a computational—that is a functional-system. Thus, computation would exist even if computers didn't—this is where critiques like those of Searle's (1990) miss the point. The fact that an existing physical computer is, as he puts it, "just a hunk of junk" is neither here nor there. Once the system can move between states and store them it's a Turing machine, Post machine, or Lambda calculus (Church, 1936)—which for these purposes don't have any significant differences between them. All such functional states are computational states—defined by the moving from one state to another. Knowledge—and it doesn't matter here if we are talking about humans, other animals, or

even plants, is therefore the acquiring of usable local regularities. An ecology, in other words. Evolution has produced systems that predict things about their environments (brains) that sometime hang out together in social groups. But all of these things are computational states—and adding ecology to the complete picture does not change this fact. Indeed, it deepens it by showing how affordances must be part of the complete functional picture. Indeed, as Barrett et al. (2014, 2015) are showing, the minimalist bet of some branches of cognitive science—e.g., that we could completely capture the functionalist understanding of the organism without seeing the details of the system it lives in, may well turn out to be false. It turns out that we do need to understand how an organism responds to affordances, that the functional details of perceptual organization matter, and so forth.

But, since we are all functionalists, we really have very good reason to all get along. If it really is functionalism all the way down—then there is no radical split to be had between functional models and the ones Barrett et al. (2015) espouse. What she and her colleagues have done is draw attention to the need for (computational) systems to be closely connected to their ecologies. Specifically, that perception and cognition indeed need to be closely related (Barrett, 2011, p.22). It might be noted that, in this, she echoes the call of Brooks (1990) whose use of the concept of subsumption layers reminds us that one way to escape the representational issue in artificial systems is to make the system use the real world as its model and in this they offer a much needed route to allow affordances to enter into the modeling. Functionalism isn't just the only game in town. It's the only game in any ecology.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

ACKNOWLEDGMENTS

I am indebted to Gary Marcus for conversations which partly led to this article.

REFERENCES

Barrett, L. (2011). *Beyond the Brain: How Body and Environment Shape Animal and Human Minds*. Princeton, NJ: Princeton University Press.

Barrett, L., Pollet, T. V., and Stulp, G. (2014). From computers to cultivation: reconceptualizing evolutionary psychology. *Front. Psychol.* 5:867. doi: 10.3389/fpsyg.2014.00867

Barrett, L., Pollet, T. V., and Stulp, G. (2015). Evolved Biocultural beings (who invented computers). *Front. Psychol.* 6:1047. doi: 10.3389/fpsyg.2015.01047

Boole, G. (1854). *An Investigation of the Laws of Thought: On Which Are Founded the Mathematical Theories of Logic and Probabilities*. New York, NY: Dover Publications.

Brooks, R. A. (1990). Elephants don't play chess. *Rob. Auton. Syst.* 6, 3–15. doi: 10.1016/S0921-8890(05)80025-9

Chalmers, D. J. (1996). *The Conscious Mind: In Search of a Fundamental Theory*. New York, NY: Oxford University Press.

Church, A. (1936). An unsolvable problem in elementary number theory. *Am. J. Math.* 58, 345–363.

Corcoran, J. (2003). Aristotle's prior analytics and boole's laws of thought. *Hist. Philos. Logic* 24, 261–288. doi: 10.1080/0144534031000160470 7

Daugman, J. G. (2001). "Brain metaphor and brain theory," in *Philosophy and the Neurosciences: A Reader*, eds W. P. Bechtel, P. Mandik, J. Mundale, and R. S. Stufflebeam (Oxford: Blackwell).

de La Mettrie, J. O. (1960). *L'Homme Machine (Man a Machine)*. Princeton, NJ: Princeton University Press (Originally published in 1748).

Moravec, H. P. (2000). *Robot*: *Mere Machine to Transcendent Mind*. Oxford: Oxford University Press on Demand.

von Neumann, J., and Burks, A.W. (1966). *Theory of Self-Reproducing Automata*. Urbana, IL; London: University of Illinois Press.

Rescorla, R. A., and Wagner, A. R. (1972). A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. *Class. Cond. II Curr. Res. Theory* 2, 64–99.

Searle, J. R. (1990). Is the brain's mind a computer program. *Sci. Am.* 262, 26–31. doi: 10.1038/scientificamerican0190-26

Turing, A. M. (1950). Computing machinery and intelligence. *Mind* 59, 433–460. doi: 10.1093/mind/LIX.236.433

Van Hasselt, H., Guez, A., and Silver, D. (2015). *Deep Reinforcement Learning with Double Q-Learning*. CoRR, abs/1509.06461.

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

HYPOTHESIS AND THEORY
published: 01 September 2015
doi: 10.3389/fnins.2015.00303

Functional constraints in the evolution of brain circuits

Conrado A. Bosman[1,2]* *and Francisco Aboitiz*[3]

[1] *Cognitive and Systems Neuroscience Group, Swammerdam Institute for Life Sciences, Center for Neuroscience, Faculty of Science, University of Amsterdam, Amsterdam, Netherlands,* [2] *Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Santiago, Chile,* [3] *Departamento de Psiquiatría, Centro Interdisciplinario de Neurociencia, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile*

Regardless of major anatomical and neurodevelopmental differences, the vertebrate isocortex shows a remarkably well-conserved organization. In the isocortex, reciprocal connections between excitatory and inhibitory neurons are distributed across multiple layers, encompassing modular, dynamical and recurrent functional networks during information processing. These dynamical brain networks are often organized in neuronal assemblies interacting through rhythmic phase relationships. Accordingly, these oscillatory interactions are observed across multiple brain scale levels, and they are associated with several sensory, motor, and cognitive processes. Most notably, oscillatory interactions are also found in the complete spectrum of vertebrates. Yet, it is unknown why this functional organization is so well conserved in evolution. In this perspective, we propose some ideas about how functional requirements of the isocortex can account for the evolutionary stability observed in microcircuits across vertebrates. We argue that isocortex architectures represent canonical microcircuits resulting from: (i) the early selection of neuronal architectures based on the oscillatory excitatory-inhibitory balance, which lead to the implementation of compartmentalized oscillations and (ii) the subsequent emergence of inferential coding strategies (predictive coding), which are able to expand computational capacities. We also argue that these functional constraints may be the result of several advantages that oscillatory activity contributes to brain network processes, such as information transmission and code reliability. In this manner, similarities in mesoscale brain circuitry and input-output organization between different vertebrate groups may reflect evolutionary constraints imposed by these functional requirements, which may or may not be traceable to a common ancestor.

Keywords: cortical evolution, canonical microcircuits, neuronal oscillations, predictive coding, cortical neurodevelopment

OPEN ACCESS

Edited by:
Robin Clark,
University of Pennsylvania, USA

Reviewed by:
Paul M. Nealen,
Indiana University of PA, USA
Roberto Limongi,
Diego Portales University, Chile

***Correspondence:**
Conrado A. Bosman,
Cognitive and Systems Neuroscience Group, Swammerdam Institute for Life Sciences, Center for Neuroscience, Faculty of Science, University of Amsterdam, Science park 904, 1098 XH Amsterdam, Netherlands
c.a.bosmanvittini@uva.nl

Specialty section:
This article was submitted to Evolutionary Psychology and Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *30 June 2015*
Accepted: *10 August 2015*
Published: *01 September 2015*

Citation:
Bosman CA and Aboitiz F (2015) Functional constraints in the evolution of brain circuits. Front. Neurosci. 9:303. doi: 10.3389/fnins.2015.00303

Introduction

A noticeable feature observed in the central nervous system is its well-conserved organization across species. In vertebrates, pallial circuits (i.e., those in the superior aspect of the cerebral hemispheres) are functionally arranged through the interaction of excitatory and inhibitory neurons across multiple cortical layers (Lorente de No, 1938). According to this organization, excitatory neurons often have longer projections that allow the communication and information transfer between several brain areas and effectors. Inhibitory neurons have shorter projections,

are mostly locally connected and are able to modulate excitatory forces, by imposing recurrent periods of neuronal inhibition, which are followed by transient windows of excitation (Isaacson and Scanziani, 2011; Kepecs and Fishell, 2014; Siegle et al., 2014). This reciprocal connectivity is at the basis of several computational mechanisms observed during brain functioning.

Remarkably, neurons do not connect randomly. Excitatory and inhibitory neurons are organized in relatively well-defined neuronal microcircuits, an organization that expands the computational possibilities of single units. Several comparative anatomical studies have consistently shown that these basic organizational principles are generally present across vertebrate classes and can be found across distant phyla, despite noticeable macroscopic anatomical differences (Shepherd, 2011; Ahumada-Galleguillos et al., 2015). This architectural stability has led some authors to consider this organization as canonical and to propose that these regularities are critical for sensory and cognitive processing (Douglas and Martin, 2004), a concept that traces back to the notion of "cortical unit" (cortical column, or mini-column) originally proposed by Mountcastle, and elaborated upon by Hubel and Wiesel. These early authors postulated the notion of a fundamental computational unit, upon which cortical functions could be elaborated incrementing the number of available units (Hubel and Wiesel, 1977; Gilbert, 1983; Mountcastle, 1997). However, an important—but yet unsolved—question to elucidate from an evolutionary perspective is whether a canonical microcircuit has evolved from a common ancestor or, alternatively, it represents a case of parallel or convergent evolution. In other words, what are the determinants of such canonical structure in evolution and are these determinants evolved from a common ancestor? In this article, we aim to outline an answer to these questions, presenting some ideas that may help to understand how it is possible to observe similar functional microcircuit architectures—despite substantial differences in macroscopic brain anatomy—, without the necessity to refer a common ancestor across different lineages.

Previously, we proposed that actual architectures of the mammalian brain rely on highly conserved neurodevelopmental mechanisms (Aboitiz and Montiel, 2007b; Bosman et al., 2014). Natural selection may have differentially modulated the expression and regulation of these neurodevelopmental mechanisms according to contingent adaptations, thus producing gross morphological differences across lineages (Aboitiz and Montiel, 2007b). Additionally, we suggested that a very basic excitatory-inhibitory interplay is a fundamental functional motif, which has been exploited through evolution to bear synchronized rhythmic activity through multiple brain architectures. Further, neuronal synchronization mechanisms might have evolved to support several neuronal computations, which are ultimately responsible of several high-level functions observed in the brain (Bosman et al., 2014; Womelsdorf et al., 2014). Here, we expand these previous concepts arguing that, despite neurodevelopmental differences produced by contingent adaptations, the canonical microcircuit organization is observed as a recurrent motif across evolution. This recurrence is the consequence of functional constraints imposed by the connectivity derived from canonical microcircuits. In turn, the compartmentalization of neuronal rhythms configures an optimized solution for advanced computational processing, a necessary adaptation for species to survive in an increasingly complex world.

Synchronization of cortical oscillations subserves several important cortical functions like gain control, postsynaptic coincidence detection of presynaptic spikes, phase coding, regulation of spike timing by inhibition, and routing of information among others (Fries, 2005, 2009; Singer, 2013; Bosman et al., 2014; Womelsdorf et al., 2014). Also, neuronal rhythm synchronization has been found consistently across different species and brain structures (Buzsáki et al., 2013; Bosman et al., 2014). Because of this ubiquity, some authors have considered synchronized oscillations merely a proxy for excitatory-inhibitory interactions (Merker, 2013; Ray and Maunsell, 2015), whereas others considered neuronal synchronization a fundamental computational principle (Fries, 2009; Bosman et al., 2014). Nevertheless, wide evidence sustains the notion that oscillatory phase-based relationships allow dynamic modulation in different brain structures (Engel et al., 2001; Salinas and Sejnowski, 2001; Varela et al., 2001; Fries, 2009; Bressler and Menon, 2010; Donner and Siegel, 2011; Singer, 2013; Bosman et al., 2014; Womelsdorf et al., 2014). Moreover, it has been recently proposed that neuronal oscillations can play a major role in predictive coding strategies (Bastos et al., 2012), which are pivotal in the implementation of inferential functionality in the brain (Rao and Ballard, 1999). From an evolutionary perspective, we argue that oscillatory synchronization may have been decisive in the evolution of cortical microcircuits. Oscillations may have imposed functional constraints to the circuitry architecture, and led to converge in canonical organization. Importantly, their acquisition may or may not be homologous across taxa. For example, in large-brained vertebrates, like mammals and birds, a shared canonical microcircuit may represent an ancestral condition, or alternatively, it may have emerged independently in both lineages. Whatever the case, we aim to show that the early acquisition of rhythmic synchronization patterns may have constrained the evolution of microcircuits and, in this manner been involved in the convergence of a particular canonical architecture. It is useful at this point to delineate the breadth of the concepts that we will discuss in this review. The term "mechanism" used in describing these circuits is primarily computational (e.g., communication through coherence), rather than synaptic (e.g., based upon plasticity of conductances). We used the term "constraint" as usually depicted in evolutionary contexts, normally interpreted as a stasis of features due to limited evolutionary plasticity, as opposed to a stasis of features due to common functional demands.

In the following sections, we will compare the multilayer organization in the brain between mammals and sauropsids (birds and reptiles together comprise a taxon called sauropsida). We will argue that those three lineages show a similar pattern of cortical connectivity, despite substantial differences in their neuronal development. Then, we will review how oscillations can emerge from a multi-layered organization and exert modulatory influences across cortical hierarchies,

indicating a powerful functional constraint for this shared microcircuit.

The Canonical Microcircuit in Mammals and Other Species

The mammalian isocortex is part of the pallium—the "roof" of cerebral hemispheres—that also includes the hippocampus, the olfactory cortex and parts of the amygdala. Lorente de No early established that despite number, cell form and size variations, the structural details of the isocortex remains constant across species (Lorente de No, 1938). Contrasting with other pallial regions, the isocortex is characterized by a six-layered organization, characterized by a central layer (layer 4, L4), containing inhibitory and excitatory neurons that receive most of the thalamic input (**Figure 1A**). These neurons target mostly interneurons and fibers of layers 1 and 2, providing feedforward inhibition to the cortico-cortical connections present in this layer (Shepherd, 2011). L2 and L3 contain pyramidal cells that receive synaptic inputs from local interneurons and excitatory neurons from L4. Their axons project to other cortical regions. L1, L2, and L3 comprise the supragranular layers. Conversely, L5 and L6 encompass infragranular layers. L5 contains large pyramidal cells, which project to subcortical structures or, as in the motor cortex, to the spinal cord trough the internal capsula. L6 provides efferent connections to the thalamus via small pyramidal cells. Both layers receive synaptic inputs from collateral projections of L3 neurons and inhibition by local interneurons (Lorente de No, 1938; Shepherd, 2011; Harris and Shepherd, 2015).

Neurons configuring this circuit are organized into radial columns of clonally related cells that cross all these layers (Mountcastle, 1997; Noctor et al., 2001). Furthermore, sibling neurons within a cortical column are preferentially interconnected among themselves, showing similar stimulus feature selectivity (Li et al., 2012); and this microcircuit assembly is mediated by transient electrical couplings among sister neurons (Yu et al., 2012). More recently, it has been found that the unique inside-out developmental gradient of the mammalian isocortex, partly determined by the reelin signaling pathway, is a key regulator of this lineage-dependent columnar microcircuit (He et al., 2015). This evidence indicates that the assembly of the isocortical canonical microcircuit is strongly dependent on developmental factors unique to mammals, even if there are general patterning mechanisms that are shared with other vertebrates (Aboitiz, 2011). Thus, the specific development of similar circuitries in other amniotes may rely on different, but convergent developmental mechanisms. Functionally, cortical columns depict clear excitatory-inhibitory relationships across neuronal constituents, which facilitates information transfer processes and oscillatory dynamics. In the original description of canonical microcircuits (**Figure 1B**), Douglas and Martin (1991) aimed to explain how transient stimulation of the visual cortex of the cat produced cortical fast excitatory currents followed by slow, long-lasting inhibition. They described a model using intrinsic excitatory-inhibitory relays observed in L4 are able to modulate transient activities derived from thalamic inputs thus providing major substantial excitation, which can be transferred to infra and supragranular layers, where further processing beyond pulsatile stimulation activity can take place (Douglas and Martin, 1991). Furthermore, dynamic canonical microcircuits based in the same inhibitory-excitatory relationships have been related to several important computational processes (Bosman et al., 2014; Womelsdorf et al., 2014). For instance, canonical microcircuits architectures are relevant implementing feedback and feedforward inhibition. Feedback inhibition has been implicated in the origins of high-frequency oscillations (Cardin et al., 2009; Siegle et al., 2014). Conversely, feedforward inhibition has a major role implementing gain control and divisive normalization (Wilson et al., 2012). These computational processes are at the basis of several important sensorial and cognitive functions (Bosman et al., 2014; Womelsdorf et al., 2014), and canonical microcircuits provide a basic connectivity motif that accounts for these computations (Douglas and Martin, 2004; Shepherd, 2011).

Yet, this description leaves unanswered the question whether this architecture derives from a primitive ancestor common to

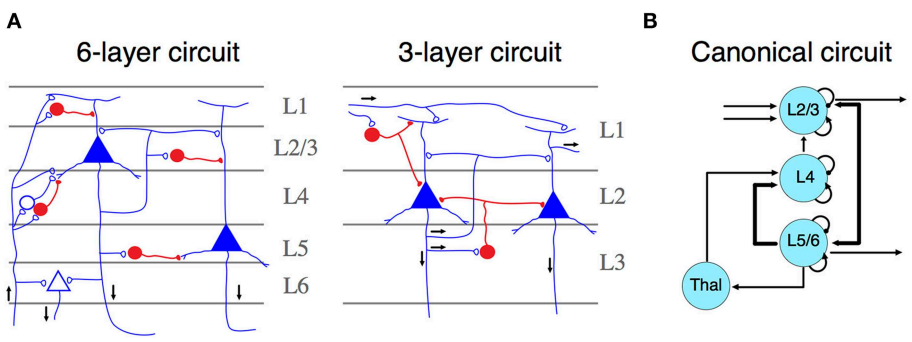


FIGURE 1 | (A) Simplified representation of a six- (left) and three- (right) layer microcircuit. Neurons depicted in blue (open synapses) are excitatory cells, whereas neurons in red (close synapses) are inhibitory ones. Black arrows represent the flow of information across different layers. Both panels adapted from Shepherd (2011). **(B)** Schematic representation of a canonical microcircuit. Arrows represent connectivity within nodes, ordered spatially according to their anatomical localization. Curved arrows illustrate intrinsic (excitatory and inhibitory) connectivity. Adapted from Douglas and Martin (2004).

other vertebrates. This question can be addressed by comparing the mammalian microcircuit architecture with those observed in birds, reptiles (sauropsids, the sister taxon of mammals) or perhaps more important, modern amphibians, whose brains are morphologically more similar to that of the putative common amniote ancestor (shared common ancestor with sauropsids and mammals). Unfortunately, there is yet little evidence on circuit organization in amphibians, and we will have to rely on evidence recently gathered in reptiles and birds.

Connectivity and Development of Mammalian and Sauropsidian Brains

The isocortex has six layers and radial input organization. It differs in its overall organization from other cortices like the hippocampal region and the olfactory cortex, which display a three-layered organization and a tangential organization of inputs, (**Figure 1A**) (Nieuwenhuys, 1994). In reptiles, some cortical structures fit the design of three-layered structures. However, other pallial components, namely the dorsal ventricular ridge (DVR), depict a nuclear appearance, resembling parts of the mammalian amygdalar complex. In birds, the DVR is roughly subdivided into a nidopallium and a mesopallium among other structures. Comparing with other regions of the pallium, it becomes a highly differentiated structure that comprises much of the auditory and visual sensory inputs to the brain. This projections make the DVR complex the main sensory processing structure in birds (for review see Aboitiz and Montiel, 2007b).

Despite the observed differences in laminar vs. nuclear organization of the mammalian isocortex and the avian nidopallium, respectively, Harvey Karten described in 1960's similar processing circuits in these two structures. These similarities led Karten to postulate the "equivalent cell hypothesis," asserting that this circuit was homologous in birds and mammals (Karten, 1968, 1969). From this hypothesis, it follows that the nidopallium of birds is homologous to parts of the mammalian isocortex, i.e., both derive from a same structure in a common ancestor (Karten, 2013, 1997), an assertion that has been recently challenged (see below). Recent studies have provided some evidence that can be interpreted in favor of this hypothesis. For instance, auditory circuits in birds depict sensory thalamic projections targeting a region termed Field L2, which correspond to the isocortical L4. L2 neurons project to Field L1 (and the caudal mesopallium), and to L3, corresponding to supragranular and infragranular isocortical layers, respectively (Wang et al., 2010), mimicking the canonical organization observed in columnar circuits. A similar "columnar-type" organization has been described in the visual DVR of the chick (Ahumada-Galleguillos et al., 2015). Recently, Calabrese and Woolley (2015) investigated the electrophysiological properties of the auditory DVR in birds, and compared this evidence with the known properties of different isocortical layers. They observed similarities between birds and mammals in the latencies, noise correlations, and coding strategies of the different components of this microcircuit. Additionally, it was observed that afferent connections of neurons projecting to the thalamus express similar neurochemical markers (i.e., EAG and RORB) in different pallial regions of mammalian, reptilian, and avian brains. Conversely, output projection neurons of different pallial regions express the marker Er81 in both mammals and sauropsids (Dugas-Ford et al., 2012). However, it should be noted that while this evidence compellingly indicates the existence of common input-output neuronal phenotypes in different pallial regions across amniotes, it does not necessarily imply that the avian nidopallium is homologous to the mammalian isocortex as a region (Aboitiz and Zamorano, 2013).

The above interpretation has been challenged by some authors who argue that the avian nidopallium (and mesopallium) and the mammalian isocortex have different developmental origins, i.e., the isocortex derives from embryonic dorsal pallial components while the nidopallium and mesopallium derive from ventral and lateral pallial components (Aboitiz, 1992, 1995; Striedter, 1997; Fernandez et al., 1998; Puelles et al., 1999, 2000; Medina and Abellán, 2009). More recently, it has been suggested that the isocortex shares with the avian nidopallium a common genetic determinant—tentatively driven by a Pax6-dependent cascade (Georgala et al., 2011), and the expansion of both structures is largely based on the amplification of similar genetic mechanisms (Aboitiz and Montiel, 2007a; Aboitiz, 2011; Aboitiz and Zamorano, 2013). This evidence suggests the existence of a continuous overlap of dorsal and ventral morphogenetic signals that drives the regional differentiation of pallial regions (Hoch et al., 2009), rather than parcellating the embryonic pallium in discrete components. Furthermore, these morphogenetic signals have been differentially modulated in mammals and sauropsids, resulting in the expansion of the DVR in the ventral and lateral pallium of sauropsids, and in the expansion of the isocortex in the dorsal pallium of mammals, respectively (Aboitiz, 2011; Aboitiz and Zamorano, 2013). Similarly, Luzzati and coworkers (Luzzati et al., 2009; Luzzati, 2015) have advanced the hypothesis that the emergent isocortex of early mammals co-opted genetic pathways involved in lateral pallial (i.e., olfactory cortex) differentiation and activated them in the neocortical proliferative epithelium to yield the supragranular neuronal phenotypes.

Thus, the weight of the developmental and genetic evidence indicates that the mammalian isocortex and the avian nidopallium originated as expansions of different embryonic regions present in the common ancestor, possibly through differential amplification of telencephalic signaling centers that are shared in both taxa. This, again, is consistent with structural and functional convergence between these structures, rather than homology.

Tangential Networks in the Isocortex and Other Cortices

Another approach regarding the ancestral circuitry of mammals and sauropsids (in this case, reptiles) has highlighted the similarities in tangential organization of the mammalian isocortex and olfactory cortex, together with that of the reptilian cortical structures (Lynch, 1986; Shepherd, 2011; Rowe and Shepherd, 2015). In this scenario, the isocortex is primarily a tangentially associative network, where afferents were ancestrally located in the superficial marginal zone, running parallel to the cortical surface and contacting several pyramidal cell apical dendrites in tandem. The now characteristic radial,

columnar isocortical organization was possibly a late innovation, concomitant with the differentiation of primary sensory areas and the development of the subplate. The subplate served as a substrate for thalamic axonal growth in the white matter underlying the cortical plate (Aboitiz et al., 2005). In line with this hypothesis, several authors have very recently highlighted striking connectional and functional similarities between the mammalian olfactory cortex and the reptilian dorsal cortex (the latter deriving from the dorsal pallium, and the likely regional homolog of the mammalian isocortex), both exhibiting similar laminar organization and an apparent poor topographic mapping of the sensory surfaces (Fournier et al., 2015; Naumann et al., 2015; Rowe and Shepherd, 2015). This indicates a shared combinatorial and associative array in both structures. Early studies in the isolated dorsal cortex of the turtle describe intrinsic circuit properties that resemble very much those observed in mammalian isocortex. Compared with mammalian isocortex, the dorsal cortex circuitry is simpler. It consists basically in two types of neurons, pyramidal and stellate cells. Thalamic inputs usually target pyramidal cells to elicit volleys of excitatory activity that it is further controlled by feedforward inhibition (Smith et al., 1980). Remarkably, intrinsic long-lasting inhibition is observed after stimulation (Kriegstein and Connors, 1986), similar to those responses observed in cat visual cortex and other mammals (Douglas and Martin, 1991; Shepherd, 2011). Furthermore, Fournier et al. (2015) called attention to the oscillatory activity of cortical networks in both reptiles and mammals, emphasizing activity in the beta range (15–35 Hz), which in the olfactory cortex appears to be involved in discrimination learning and pattern completion, while in the reptilian dorsal cortex has been tentatively associated to spatial processing. These authors suggest that beta frequencies are involved in long-range networks that participate in coding for stimulus selectivity. This evidence suggests a likelihood of convergence over strict homology and it is in agreement with our original proposal about the consequences of the development of an associative olfactory-hippocampal in the origin of the laminar isocortex (Aboitiz et al., 2003; Aboitiz and Zamorano, 2013). Particularly, we consider the use of the olfactory-hippocampal axis as an interface of the dorsal pallium in reptiles. When as it expanded, it was able to recruit different sensory systems in this network.

How Complex were the Ancestral Microcircuits?

The analysis of neurodevelopmental constraints unveils two possible mechanisms that can explain the evolution of the isocortex. So far, the evidence for a common microarchitecture in the avian and mammalian brains suggests the possibility of an ancestral microcircuit present in pallial structures, of all amniotes. However, the alternative explanation of evolutionary convergence is also likely. In both scenarios, the architectural circuit stability of a canonical microcircuit may be the result of phylogenetically parallel elaborations on a quite simple, basic input-output organization driven by functional and/or developmental constraints, as there are not many ways to perform early processing of sensory input, and there are not many developmental or genetic pathways to achieve this organization. It is therefore important to elucidate the specific characteristics of this putative ancestral circuit.

Some macroscopic features of a primitive telencephalon may help to understand the organization of a very simple ancestral circuit. The rudimentary telencephalon of early amniotes was a quite a small tubular structure (Kielan-Jaworowska et al., 2004; Rowe and Shepherd, 2015), perhaps more similar in morphology to the telencephalon of present amphibians, who display a very limited degree of radial neuronal migration and a conspicuous tangential arrangement of inputs in the superficial or molecular layer. Furthermore, both within therians (placental and marsupial mammals) and within sauropsids, an increase in complexity can be observed from more basal forms to more derived forms, associated with the development of an embryonic subventricular zone housing intermediate progenitor neurons (Cheung et al., 2010). Therefore, it is quite likely that this basic processing circuit became increasingly complex independently in both lineages, concomitant with larger brain sizes and more complex behaviors.

A basic characteristic of the canonical microcircuit is the balanced interplay between excitation and inhibition (van Vreeswijk and Sompolinsky, 1996; Isaacson and Scanziani, 2011). This balanced activity represents the basis of complex neuronal responses embedded in microcircuits (Salinas and Sejnowski, 2001; Tiesinga and Sejnowski, 2009; Isaacson and Scanziani, 2011; Womelsdorf et al., 2014). Inhibitory interneurons may have served to regulate the oscillatory dynamics of such primordial circuits (Tiesinga and Sejnowski, 2009). Accordingly, a rudimentary circuit architecture, organized through input receiving and output sending neurons, with intermediate associative excitatory neurons and inhibitory interneurons providing feedforward and lateral interactions, is very likely to have existed in pallial regions of the ancestral amniote (see also Rowe and Shepherd, 2015). It is possible though, like in the reptilian cortex, that input and output neurons were tangentially separated (Dugas-Ford et al., 2012). Although maintaining this same general architecture, the processing microcircuits of the mammalian isocortex, the nido- and the mesopallium of birds are very likely much more complex than this, including larger numbers of excitatory and inhibitory interneurons, compartmentalization of information and well-organized interareal communication.

Large Scale Organization of Mammalian Microcircuits

In larger brain sizes, as it is observed in mammals, canonical microcircuits are embedded in hierarchically organized neuronal networks. Remarkably, adjacent areas shown strong regularities in their laminar organization and interareal connectivity, a feature recently observed in recent anatomical studies of primate visual cortex, using retrograde tracers combined with electrophysiological techniques (Markov et al., 2014). These studies depict a basic organization of the connectivity of microcircuits across areas. Feedforward projections originate in neurons of supragranular layers of "lower-order" areas (i.e., V1 or closer to it) and target granular neurons of L4 of "higher-order" areas (i.e., successively farther from V1) (Lund, 1988;

Felleman and van Essen, 1991; Markov et al., 2014). Conversely, feedback projections depart from infragranular layers of higher order areas, to end in the proximities of L4 of lower order areas (Markov et al., 2014). Based on these regularities, several attempts of modeling these anatomical networks have been performed (Felleman and van Essen, 1991; Markov et al., 2014). Recent models have emphasized the existence of a *bow-tie* network architecture with a processing core—areas that share connections for multiple origins—with several independently connected sensory areas (Ercsey-Ravasz et al., 2013). In this model, interareal connectivity patterns are compatible with both, long-range connection distribution and local microcircuit architectures (Markov et al., 2013). Alternative models of organization emphasize a *small-world* network architecture, in which hierarchies are distributed across hubs or regions receiving a high number of connections (see Bullmore and Sporns, 2009). These features facilitate wire-length minimization in concomitance with increasing communication efficiency, leading to an overall increase in neocortical computations associated with a reduction in energy consumption (Bullmore and Sporns, 2012; Ercsey-Ravasz et al., 2013; Markov et al., 2014). This leads us to the hypothesis that these computational advantages may have been functionally constrained the evolution and convergence of these cortical hierarchies across phyla.

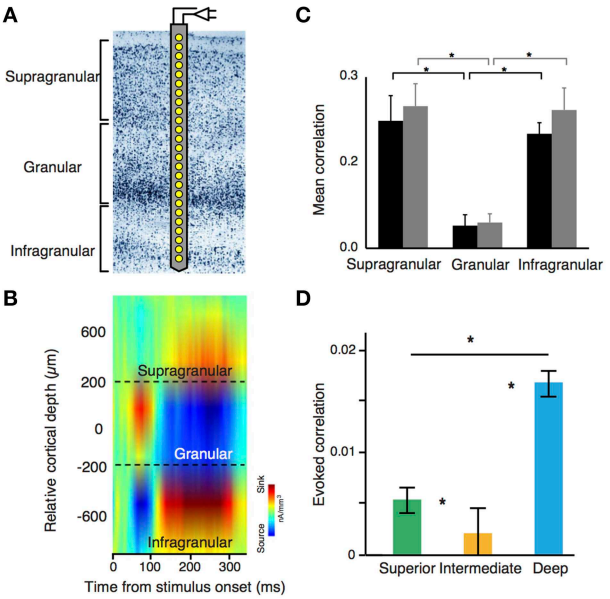


FIGURE 2 | (A) Laminar recording on visual cortex using a linear microelectrode array (LMA). **(B)** Stimulus-evoked current source density (CSD) analysis using laminar probes. LMAs typically depict sinks (cation inflow from the extracellular to the intracellular space, in red) and sources (cation outflow from the intracellular to the extracellular space, in blue) of neuronal activity. This configuration pattern is useful to segregate differential layer activity. **(C)** Noise correlation amplitude is significantly lower in granular layers as compared with supra and infragranular layers. Black and gray bars denote two different monkeys. **(B,C)** adapted from Hansen et al. (2012). **(D)** Decrease of noise correlations amplitude in cyto-architectonically defined intermediate layers of the songbird auditory caudal meso/nidopallium cortex [Asteriks indicate significant differences in correlations between regions ($p < 0.05$, Kruskal-Wallis test with multiple comparisons correction)]. Adapted from Calabrese and Woolley (2015).

Dynamic Activity of Laminar Microcircuits

The understanding of the neuronal dynamics generated in canonical microcircuits has been facilitated by the popularization of techniques that enable simultaneous recordings through multiple areas and cortical layers (Lewis et al., 2015). Linear microelectrode (LMAs) feature several contact points through one or multiple shanks (**Figure 2A**). This configuration facilitates recordings of neuronal activity—spikes and local field potentials (LFP)—simultaneously across layers. In animals, high-density electrocorticograms (ECoGs) arrays can be used to study cortical LFP-LFP interactions across different brain areas. In LMAs, LFPs are usually studied using current source density (CSD) analysis, a technique amendable to give access to the sinks and sources of voltage differences at the extracellular space (Mitzdorf, 1985). CSD analysis can be used to identify electrode position based on the different profiles obtained at different layers (**Figure 2B**). Additionally, the temporal coordination between spikes and LFPs can be described using spike-field coherence based techniques, which quantify the phase relationships between the ongoing LFP and spike activity. All these techniques are especially advantageous for the study of long-range interactions across cortical microcircuits (Lewis et al., 2015).

Noise Correlations and Dynamic Structure of Microcircuits

Many of the studies using LMAs have focused on understanding the dynamics of neuronal assemblies using noise and stimulus correlations, which are two important measures of the conjoined variance among neurons (Averbeck and Lee, 2004). Noise correlations quantify the common variance of a neuronal population that cannot be explained by any external input, representing a default "common response" from a particular neuronal population. Since noise correlations are very much dependent of the anatomical connectivity pattern through the laminar cortex, these measurements can be used to disentangle the basic functional connectivity across neurons. In mammals, it has been well observed that the intensity of noise correlations is not equally distributed across all layers and cell types (Ecker et al., 2010; Renart et al., 2010; Hansen et al., 2012; Smith et al., 2013). In rodents and primates, L2/3, L5, and L6 show high intensity of noise correlations. In contrast, L4—the main target of thalamic projections—shows little or insignificant amounts of noise correlations, and correlations between interneurons are stronger than those between pyramidal cells in both supra and infragranular neuronal populations (Hansen et al., 2012; Smith et al., 2013) (**Figure 2C**). Notably, this organization pattern seems to be present in circuits from auditory DVR nuclei in birds. Here, noise correlations are stronger in "superficial" and "deep" layers of the nuclei, but weak in the intermediate ones (Calabrese and Woolley, 2015) (**Figure 2D**). This profile is also consistent with previous proposals about the origin of noise correlations. In mammals, cortical horizontal connections—more abundant in supra and infragranular layers—are responsible of noise

correlations (Ecker et al., 2010; Renart et al., 2010). In both, avian and mammalian laminar structures, deep layers or their equivalents are densely interconnected and both groups show stronger spontaneous correlations between interneurons than those observed in pyramidal cells (Calabrese and Woolley, 2015).

Importantly, the functional connectivity denoted by noise correlations can change according to the brain state of the animal. During neuronal development, noise correlations decrease its intensity as a function of aging. This decrease is accompanied by an increase of the sparseness of neuronal responses, which are dependent upon the experience acquired by the animal (Smith et al., 2015). Spontaneous activity can be less correlated once the subject is engaged in a sensory-driven task, as it is in the case in visual attention or during arousal (Vinck et al., 2015). Furthermore, arousal status of the animal can decrease the intensity of spontaneous correlations and firing rates (Vinck et al., 2015), leading to greater sparseness of neuronal responses and being indicative a change of the underlying network state. These findings indicate how noise correlations are affected if different areas can coordinate and communicate during different brain states.

In sum, noise correlations are useful to understand neuronal dynamics taking into account anatomical connectivity across different cortical layers. Mammals and birds show striking resemblances in the distribution of noise correlations across layers and neuronal types involved. These findings are compatible with canonical microcircuit architectures in these different taxa, and suggest common functional requirements. Nevertheless, a full characterization of the functional dynamics during different brain states of the animal should take in consideration the intra- and inter-laminar oscillatory dynamics.

Neuronal Oscillations and Microcircuits

Neuronal oscillations can be consistently related across several brain structures and species in a similar fashion (Buzsáki et al., 2013; Bosman et al., 2014). These relationships can be traced back to a limited set of circuit motifs, which are in turn, strongly dependent on the inhibitory-excitatory interplay presented in cortical and subcortical microcircuits (Bosman et al., 2014; Womelsdorf et al., 2014). Therefore, it is possible that neuronal oscillations may have conferred advantages for low-level system processing functions throughout evolution, and may also explain why neuronal oscillations are conspicuously found in several brain structures (Bosman et al., 2014).

Laminar recordings have consistently shown that rhythms at different frequencies are highly compartmentalized across layers. In hippocampus—a three-layer structure, resembling ancient brains—gamma oscillations (30–90 Hz) are functionally separated in two different bands (slow- and medium/fast gamma-band oscillations) that may have different properties and relate differently to the more prominent hippocampal theta waves. Slow gamma synchronizes between hippocampal areas CA3 and CA1, whereas medium/fast gamma is synchronized to rhythmic activity in the medial entorhinal cortex (Bragin et al., 1995; Colgin et al., 2009). In the three-layer DVR of turtles, a preeminence of highly coherent beta oscillations has been notified (Prechtl et al., 1997, 2000). This oscillatory activity resembles similar dynamics observed in the mammalian three-layer piriform cortex (Fournier et al., 2015). In birds, fast oscillatory bursts (500–600 Hz) are mostly generated by cells located in the outer layers of the optic tectum (OT), which mirrors that observed in the mammalian lateral geniculate nucleus (Marín et al., 2005). LFP recordings of the OT have shown a different oscillatory profile across layers. Whereas superficial layers of the OT show low gamma band oscillations, deep OT layers display three recognizable bands (alpha, low gamma, and high oscillations) (Sridharan et al., 2011). Importantly, these gamma oscillations are mostly locally generated and the microcircuit architecture and neuronal involvement underlying this generation are similar to those described in mammals (Goddard et al., 2012). Since OT neurons project to different pallial structures, these differences may have deep consequences in the implementation of avian cognitive abilities such as attention and visual discrimination (Sridharan and Knudsen, 2015). To the best of our knowledge, no specific studies linking LFP oscillation dynamics and pallial structures have been performed yet. Nevertheless, the similarities in anatomical connectivity and noise correlations pattern described by Calabrese and Woolley (2015) are highly indicative of similar oscillatory profiles. In mammalian visual areas, gamma oscillations have been consistently found in supragranular layers (Buffalo et al., 2011; Xing et al., 2012; Roberts et al., 2013; van Kerkoerle et al., 2014), while alpha (8–12 Hz) and beta have been recorded in infragranular layers (Lopes Da Silva and Storm Van Leeuwen, 1977; Bollimunta et al., 2008; Buffalo et al., 2011; Spaak et al., 2012; van Kerkoerle et al., 2014), a finding compatible with earlier *in vitro* studies showing pyramidal cells spontaneously oscillating at 12 Hz in this layer (Silva et al., 1991).

What could be the advantage of having compartmentalized oscillations? In the isocortex, synchronization of local neuronal assemblies can lead to rhythmic synchronization across cortical regions (Buschman and Miller, 2007; Gregoriou et al., 2009; Bosman et al., 2012; Salazar et al., 2012; Jia et al., 2013). If interareal synchronization can serve as a mechanism of dynamic communication across brain areas (Fries, 2005; Bosman et al., 2012), then compartmentalized oscillations may contribute to segregate the information received from feedback and feedforward projections on a given area. This hypothesis has been evaluated in two recent studies (**Figure 3**). In the first study, Bastos and colleagues measured spectral Granger causal influences across eight areas of the visual hierarchy, using intracranial electrocorticographic recordings in non-human primates engaged in a visual task (Bastos et al., 2015b) (**Figure 3A**). They observed asymmetrical influences of the directionality of different frequency bands. Gamma-band influences were mostly feedforward, whereas beta oscillations exerted feedback influences across brain areas (**Figure 3B**). Strikingly, these spectral asymmetries configured a dynamical hierarchy that correlates with the anatomical hierarchy of the explored areas (Markov et al., 2014) (**Figure 3C**). In the second study, van Kerkoerle et al. (2014) implanted LMA in areas V1 and V4 of monkeys trained in a figure-ground discrimination task. They used Granger causality, microstimulation techniques and

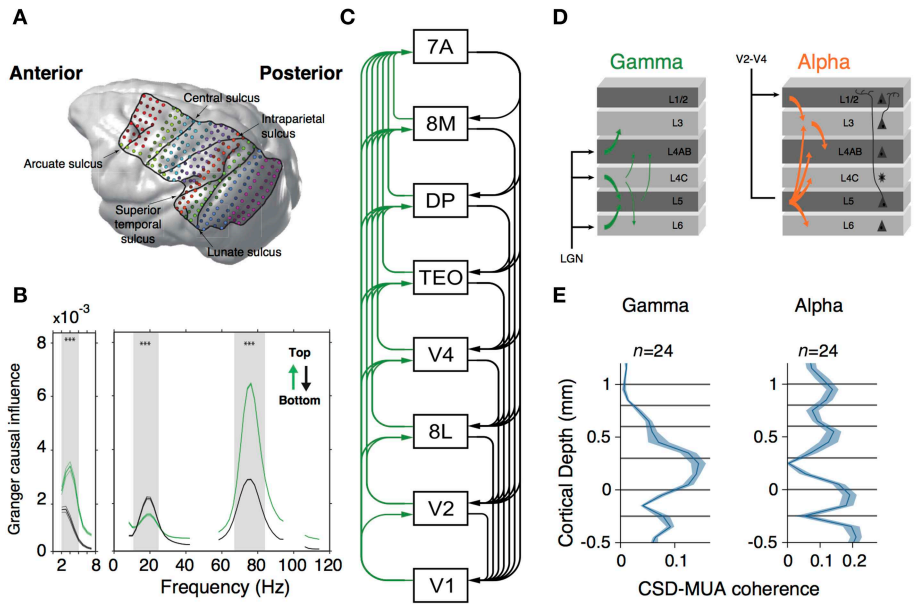


FIGURE 3 | (A) MRI-scan based rendering of a monkey brain implanted with an ECoG grid. Lines indicate the boundaries of recorded regions. Dots indicated 252 recording sites. **(B)** Granger-causal influence spectra of across all regions of interests separated for top-down (black line) and bottom-up (green line) directions. Spectral top-down influences are mostly at beta frequency-band, whereas bottom-up influences occurs at gamma frequency-band. Asterisks indicate significant differences ($p < 0.001$, randomization test). **(C)** Hierarchical ranking of recorded areas according to Markov et al. (2014). Green lines indicate bottom-up influences. Black lines denote top-down influences. **(A–C)** are modified from Bastos et al. (2015b). **(D)** Representation of Granger causality influence across layers for gamma (left) and alpha (right) frequency bands. Gamma causal influences depart from L4 to infra and supragranular layers. Alpha is mostly observed in infragranular layers and influences granular and supragranular layers. **(E)** Laminar profile of spike-field coherence (measured through the CSD-MUA coherence) for gamma (left) and alpha (right) frequency band. Middle and supragranular layers show increased gamma field coherence whereas alpha is concentrated in infragranular layers. **(D,E)** are modified from van Kerkoerle et al. (2014).

pharmacological blockade of NMDA receptors to convincingly demonstrate that gamma-band activity started its influence in the granular layers within a column, after which it propagated to the superficial and deeper layers (**Figure 3D**). Conversely, alpha-band activity triggered in superficial and deeper layers targeted granular layers (van Kerkoerle et al., 2014) (**Figure 3E**).

Despite the fact that the two frequency bands observed in the infragranular layer in the Bastos et al. (2015b) and the van Kerkoerle et al. (2014) studies are different, both suggest a putative role of oscillatory compartmentalization through cortical layers. Low frequency oscillations may convey top-down signals and exert modulatory influences downstream the cortical hierarchy. Conversely, local gamma-band oscillators may convey bottom-up modulatory signals to influence cortical activity upstream cortical hierarchy. Also, it is yet unknown how information conveyed by gamma and low-frequency oscillations can be integrated in cortical microcircuits. Perhaps, cross-frequency coupling mechanisms (von Stein et al., 2000; Canolty and Knight, 2010) may play a major role during integration. Regardless the specific underlying mechanisms involved in these processes, this specific connectivity may facilitate the implementation of specific coding strategies across cortical regions, as we will discuss in the following section.

Coding Strategies within Microcircuits

What are the basic computations supported by a canonical microcircuit? Canonical microcircuit architectures support the implementation of predictive coding and causal modeling processing (Friston, 2010; Bastos et al., 2012; Adams et al., 2013). Predictive coding based architectures can optimize information transfer to different areas based on generative models of a priori predictions and error estimation. Error estimations originated in lower areas can accumulatively correct and generate subsequent predictions. These predictions, in turn, modulate signal acquisition in early sensory cortices (Friston, 2010). As it is described by Friston and colleagues (Friston, 2010; Adams et al., 2013), error predictions are implemented in systems entailed to reduce the "free energy," an information theory concept related to the level of self-information (surprise) associated with an event (e.g., sensory data). Self-sustained biological systems (as the brain) tend to reduce the surprise associated to environmental changes, preserving their physiological variables constant across multiple changes. Thus, free energy minimization is the actual consequence of prediction error minimization. Interestingly, such models require a laminar compartmentalization to work optimally. Because free energy minimization is a homeostatic response, the conserved canonical microcircuit would set the basis for acute adaptation to uncertainty in a volatile environment.

Furthermore, a free energy minimization model can be implemented through the operation of neuronal oscillations through different cortical layers (Bastos et al., 2012). The studies of Bastos et al. (2015b) and van Kerkoerle et al. (2014) seem to suggest that compartmentalized oscillations may play a role in the implementation of predictive coding strategies in a canonical microcircuit. Their findings also suggest that low frequency oscillations such as beta- or alpha-band may convey prior prediction signals and exert their modulation in a top-down fashion. Inversely, high frequency oscillations such as gamma-band may bottom-up communicate error signals to higher cortices.

These hypotheses were tested in two recent studies that used dynamic causal modeling (DCM), a neural mass model that use predictive coding functions to mimic canonical microcircuits (Pinotsis et al., 2014; Bastos et al., 2015a). Pinotsis et al. (2014) were able to reproduce stimulus contrast dependences in neuronal responses and track their origins to the pyramidal neurons with forward projections. In the study of Bastos et al. (2015a), a DCM model implementing feedback-feedforward beta-gamma asymmetries between V1 and V4 replicated previous experimental observations obtained in monkeys during a selective attention task (Bosman et al., 2012). In both studies, the manipulation of the strength of synaptic connectivity and the excitatory-inhibitory balance across cortical columns provided critical evidence about the role of compartmentalized oscillations in the generation of both predictive coding strategies and transfer spectral functions through cortical microcircuits.

Altogether, these pieces of evidence raise an interesting question. Are the observed microcircuit similarities between different phyla a reflection of functional constraints imposed by the same predictive coding strategy? So far, no studies have tested this hypothesis, since direct comparisons between species are always difficult to establish. Nevertheless, comparative anatomical studies in homologous areas would help to identify which neuronal types and what type of connections organizes microcircuit architectures, and functional studies emphasizing the use of analogous and comparable sensorial and cognitive tasks might unveil many of the functional similarities observed between different species. Importantly, predictive coding strategies are ubiquitous in several brain areas and, as neuronal rhythms, are linked to many cognitive functions (Friston, 2010). Recently, it has been observed a link between the conserved canonical microcircuit observed in sensory areas with the asymmetry observed in the motor cortex of primates (Adams et al., 2013). This asymmetry and the computational implications for active inference (namely proprioceptive predictions) are described by Adams et al. (2013). It remains to be tested whether the stability of canonical microcircuits across evolution is related to the implementation of predictive coding strategies based on the compartmentalization of neuronal oscillations.

Discussion

In summary, neurodevelopmental and anatomical studies suggest a parallel evolution for canonical microcircuits. This evolution may be traced back to a common ancestor, although there is no compelling evidence supporting this claim. Despite the evolutionary distance between different taxa, the microcircuit architecture seems to be well conserved across species. Here, we aimed to explain this similarity, proposing that functional properties of the microcircuit have conferred evolutionary advantages that predisposed the selection of this particular architecture, even in the presence of different evolutionary contexts. We also claimed that the elementary functions derived from these canonical microcircuit architectures, namely the presence of compartmentalization of functions and neuronal oscillations, are derived from the basic excitatory-inhibitory interplay, which is a functional hallmarks of this evolutionary stability. Finally, we postulated that a basic neuronal architecture motif—proposed as a minimalist canonical microcircuit—might represent an early evolutionary solution to optimize the use of the predictive coding strategies that extent isocortical computational capacities. In other words, we expand the concept of a canonical microcircuit from just reflecting an ancestral condition, to become a pivotal functional motif in brain evolution across species. Thus, the functions of the canonical microcircuit across species support the notion of strong functional constraints associated to oscillatory activity in the evolution of the laminar or laminar-like pallium. Nonetheless, it must be noted that the developmental processes involved in the generation of canonical microcircuits may be quite different across amniotes (He et al., 2015). This suggests that this ancestral pallial circuit has been subjected to different embryological transformations in sauropsids and mammals, in order to maintain its basic architecture in the context of increasing brain size and circuit complexity but strikingly has converged into a more or less similar architecture able to support fundamental computational processes.

The ancestral canonical microcircuit can be reconstructed focusing on simpler circuit architecture of basal tetrapods like amphibians, which may better resemble the ancestral amniote condition. The functionality and connection pattern of canonical circuits in rudimentary tetrapods can contribute to unveil the principles that explain brain complexity and to understand the evolution of highly derived brains like those of mammals and birds. Moreover, a role of high frequency oscillation in sensory processes—such as odor identification and rudimentary visual processing—has been previously described in arthropods and cephalopods, among other species (cfr., Table 1 of Bosman et al., 2014, see also Bullock and Basar, 1988; Kirschfeld, 1992; Stopfer et al., 1997), providing further support for convergent origins of dynamically-balanced microcircuits.

Finally, in the context of the discussion regarding the homology or convergence of amniote canonical microcircuits, it is interesting to refer the convergent columnar microarchitecture in the retinae of mammals and flies. This did not pass unnoticed to Ramón y Cajal, who imagined a common circuit that maintained the main features of both visual systems (Cajal and Sanchez, 1915; Sanes and Zipursky, 2010). In both groups, there is a vertical arrangement consisting of three processing layers (with two sequential synapses) before the inputs leave the retina: (i) photoreceptors synapse on (ii) bipolar cells (lamina neurons in flies) that in turn feed onto (iii) ganglion

cells (transmedullary neurons in flies). In both synaptic relays, mammals and flies show strong horizontal connections that modulate the vertical transmission of inputs. Axons from ganglion cells or their fly equivalents leave the retina and project to a relay center (thalamus/midbrain and lobula complex, respectively) before reaching the telencephalon/thalamus in mammals, or the protocerebrum in flies. Although these similarities suggest that common ancestor of flies and mammals would have a complex retina, there are several reasons that preclude this option: First, the common ancestor of chordates had a brain more likely similar to that of cephalochordates, consisting of a spot of pigment cells connected directly with cerebral centers through a projection neuron, with no relay stations or signs of horizontal interactions. Second, other basal deuterostomes (hemichordates) show definitely no evidence of anything resembling a retina (Lacalli, 2004; Aboitiz and Montiel, 2007b; Suzuki et al., 2015). Third, an increase in synaptic retinal complexity can be observed within vertebrates, where the more basal agnathans (petromyzonts) display a rudimentary, two-layered retina (with receptors synapting directly ganglion cells, similarly to cephalochordates). In more advanced adult agnathans (cyclostomes) and in jawed vertebrates the retina becomes three-layered by the introduction of a bipolar cell layer between receptors and ganglion cells. Remarkably, the ontogeny of this circuit follows the same sequence as in phylogeny (Lamb, 2013). This is a good example of tight similarity due to convergence based on functional demands, in which a (retinal) canonical microcircuit has evolved independently in two different lineages, nonetheless being based on homologous, Pax-6 dependent patterning mechanisms (Gehring and Ikeo, 1999; note that this gene is also important for telencephalic patterning; see above). However, like in the mammalian isocortex, the specific mechanisms involved in the generation of similar circuits might be different in insects and vertebrates. Furthermore, ontogeny seems to follow similar steps as those acquired in phylogenetic history. Similarly, conserved pallial canonical microcircuits might be consequence of common processing requirements more than representing an ancestral condition.

Many homologous characters (like fins and hands) retain their identity despite serving different functions; however, in the case of canonical microcircuits we observe that function and structure conflate in a common phenotype, making it difficult to dissociate homology from functional convergence. In these conditions, we claim that a better approach to unveil the ancestral condition is one that combines comparative structure, function, development, and genetics.

Acknowledgments

The authors want to thank Lianne Klaver and Laura Petrina for helpful comments on earlier versions of this manuscript.

References

Aboitiz, F. (1992). The origin of the mammalian brain as a case of evolutionary irreversibility. *Med. Hypotheses* 38, 301–304. doi: 10.1016/0306-9877(92)90021-4

Aboitiz, F. (1995). Homology in the evolution of the cerebral hemispheres. The case of reptilian dorsal ventricular ridge and its possible correspondence with mammalian neocortex. *J. Hirnforsch.* 36, 461–472.

Aboitiz, F. (2011). Genetic and developmental homology in amniote brains. Toward conciliating radical views of brain evolution. *Brain Res. Bull.* 84, 125–136. doi: 10.1016/j.brainresbull.2010.12.003

Aboitiz, F., and Montiel, J. (2007a). Co-option of signaling mechanisms from neural induction to telencephalic patterning. *Rev. Neurosci.* 18, 311–342. doi: 10.1515/REVNEURO.2007.18.3-4.311

Aboitiz, F., and Montiel, J. (2007b). Origin and evolution of the vertebrate telencephalon, with special reference to the mammalian neocortex. *Adv. Anat. Embryol. Cell Biol.* 193, 1–112. doi: 10.1007/978-3-540-49761-5

Aboitiz, F., Montiel, J., and García, R. R. (2005). Ancestry of the mammalian preplate and its derivatives: evolutionary relicts or embryonic adaptations? *Rev. Neurosci.* 16, 359–376. doi: 10.1515/REVNEURO.2005.16.4.359

Aboitiz, F., Morales, D., and Montiel, J. (2003). The evolutionary origin of the mammalian isocortex: towards an integrated developmental and functional approach. *Behav. Brain Sci.* 26, 535–552. discussion: 552–285. doi: 10.1017/s0140525x03000128

Aboitiz, F., and Zamorano, F. (2013). Neural progenitors, patterning and ecology in neocortical origins. *Front. Neuroanat.* 7:38. doi: 10.3389/fnana.2013.00038

Adams, R. A., Shipp, S., and Friston, K. J. (2013). Predictions not commands: active inference in the motor system. *Brain Struct. Func.* 218, 611–643. doi: 10.1007/s00429-012-0475-5

Ahumada-Galleguillos, P., Fernández, M., Marin, G. J., Letelier, J. C., and Mpodozis, J. (2015). Anatomical organization of the visual dorsal ventricular ridge in the chick (*Gallus gallus*): layers and columns in the avian pallium. *J. Comp. Neurol.* doi: 10.1002/cne.23808. [Epub ahead of print].

Averbeck, B. B., and Lee, D. (2004). Coding and transmission of information by neural ensembles. *Trends Neurosci.* 27, 225–230. doi: 10.1016/j.tins.2004.02.006

Bastos, A. M., Litvak, V., Moran, R., Bosman, C. A., Fries, P., and Friston, K. J. (2015a). A DCM study of spectral asymmetries in feedforward and feedback connections between visual areas V1 and V4 in the monkey. *Neuroimage* 108, 460–475. doi: 10.1016/j.neuroimage.2014.12.081

Bastos, A. M., Usrey, W. M., Adams, R. A., Mangun, G. R., Fries, P., and Friston, K. J. (2012). Canonical microcircuits for predictive coding. *Neuron* 76, 695–711. doi: 10.1016/j.neuron.2012.10.038

Bastos, A. M., Vezoli, J., Bosman, C. A., Schoffelen, J.-M., Oostenveld, R., Dowdall, J. R., et al. (2015b). Visual areas exert feedforward and feedback influences through distinct frequency channels. *Neuron* 85, 390–401. doi: 10.1016/j.neuron.2014.12.018

Bollimunta, A., Chen, Y., Schroeder, C. E., and Ding, M. (2008). Neuronal mechanisms of cortical alpha oscillations in awake-behaving macaques. *J. Neurosci.* 28, 9976–9988. doi: 10.1523/JNEUROSCI.2699-08.2008

Bosman, C. A., Lansink, C. S., and Pennartz, C. M. A. (2014). Functions of gamma-band synchronization in cognition: from single circuits to functional diversity across cortical and subcortical systems. *Eur. J. Neurosci.* 39, 1982–1999. doi: 10.1111/ejn.12606

Bosman, C. A., Schoffelen, J.-M., Brunet, N., Oostenveld, R., Bastos, A. M., Womelsdorf, T., et al. (2012). Attentional stimulus selection through selective synchronization between monkey visual areas. *Neuron* 75, 875–888. doi: 10.1016/j.neuron.2012.06.037

Bragin, A., Jando, G., Nadasdy, Z., Hetke, J., Wise, K., and Buzsáki, G. (1995). Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat. *J. Neurosci.* 15, 47–60.

Bressler, S. L., and Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. *Trends Cogn. Sci.* 14, 277–290. doi: 10.1016/j.tics.2010.04.004

Buffalo, E. A., Fries, P., Landman, R., Buschman, T. J., and Desimone, R. (2011). Laminar differences in gamma and alpha coherence in the ventral stream. *Proc. Natl. Acad. Sci. U.S.A.* 108, 11262–11267. doi: 10.1073/pnas.1011284108

Bullmore, E., and Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat. Rev. Neurosci.* 10, 186–198. doi: 10.1038/nrn2575

Bullmore, E., and Sporns, O. (2012). The economy of brain network organization. *Nat. Rev. Neurosci.* 13, 336–349. doi: 10.1038/nrn3214

Bullock, T. H., and Basar, E. (1988). Comparison of ongoing compound field potentials in the brains of invertebrates and vertebrates. *Brain Res.* 472, 57–75. doi: 10.1016/0165-0173(88)90005-7

Buschman, T., and Miller, E. K. (2007). Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science* 315, 1860–1862. doi: 10.1126/science.1138071

Buzsáki, G., Logothetis, N. K., and Singer, W. (2013). Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. *Neuron* 80, 751–764. doi: 10.1016/j.neuron.2013.10.002

Cajal, S. R., and Sanchez, D. (1915). Contribución al conocimiento de los centros nerviosos de los insectos. Parte I Retina y centros ópticos. *Trab. Lab. Invest. Biol. Univ. Madrid* 13, 1–168. doi: 10.5962/bhl.title.37839

Calabrese, A., and Woolley, S. M. N. (2015). Coding principles of the canonical cortical microcircuit in the avian brain. *Proc. Natl. Acad. Sci.* 112, 3517–3522. doi: 10.1073/pnas.1408545112

Canolty, R. T., and Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends Cogn. Sci.* 14, 506–515. doi: 10.1016/j.tics.2010.09.001

Cardin, J. A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., et al. (2009). Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature* 459, 663–667. doi: 10.1038/nature08002

Cheung, A. F. P., Kondo, S., Abdel-Mannan, O., Chodroff, R. A., Sirey, T. M., Bluy, L. E., et al. (2010). The subventricular zone is the developmental milestone of a 6-layered neocortex: comparisons in metatherian and eutherian mammals. *Cereb. Cortex* 20, 1071–1081. doi: 10.1093/cercor/bhp168

Colgin, L. L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., et al. (2009). Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* 462, 353–357. doi: 10.1038/nature08573

Donner, T. H., and Siegel, M. (2011). A framework for local cortical oscillation patterns. *Trends Cogn. Sci.* 15, 191–199. doi: 10.1016/j.tics.2011.03.007

Douglas, R. J., and Martin, K. A. (1991). A functional microcircuit for cat visual cortex. *J Physiol. (Lond.)* 440, 735–769. doi: 10.1113/jphysiol.1991.sp018733

Douglas, R. J., and Martin, K. A. C. (2004). Neuronal circuits of the neocortex. *Ann. Rev. Neurosci.* 27, 419–451. doi: 10.1146/annurev.neuro.27.070203.144152

Dugas-Ford, J., Rowell, J. J., and Ragsdale, C. W. (2012). Cell-type homologies and the origins of the neocortex. *Proc. Natl. Acad. Sci. U.S.A.*109, 16974–16979. doi: 10.1073/pnas.1204773109

Ecker, A. S., Berens, P., Keliris, G. A., Bethge, M., Logothetis, N. K., and Tolias, A. S. (2010). Decorrelated neuronal firing in cortical microcircuits. *Science* 327, 584–587. doi: 10.1126/science.1179867

Engel, A. K., Fries, P., and Singer, W. (2001). Dynamic predictions: oscillations and synchrony in top-down processing. *Nat. Rev. Neurosci.* 2, 704–716. doi: 10.1038/35094565

Ercsey-Ravasz, M., Markov, N. T., Lamy, C., van Essen, D. C., Knoblauch, K., Toroczkai, Z., et al. (2013). A predictive network model of cerebral cortical connectivity based on a distance rule. *Neuron* 80, 184–197. doi: 10.1016/j.neuron.2013.07.036

Felleman, D. J., and van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cortex* 1, 1–47. doi: 10.1093/cercor/1.1.1

Fernandez, A. S., Pieau, C., Repérant, J., Boncinelli, E., and Wassef, M. (1998). Expression of the Emx-1 and Dlx-1 homeobox genes define three molecularly distinct domains in the telencephalon of mouse, chick, turtle and frog embryos: implications for the evolution of telencephalic subdivisions in amniotes. *Development* 125, 2099–2111.

Fournier, J., Müller, C. M., and Laurent, G. (2015). Looking for the roots of cortical sensory computation in three-layered cortices. *Curr. Opin. Neurol.* 31, 119–126. doi: 10.1016/j.conb.2014.09.006

Fries, P. (2005). A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn. Sci.* 9, 474–480. doi: 10.1016/j.tics.2005.08.011

Fries, P. (2009). Neuronal gamma-band synchronization as a fundamental process in cortical computation. *Ann. Rev. Neurosci.* 32, 209–224. doi: 10.1146/annurev.neuro.051508.135603

Friston, K. (2010). The free-energy principle: a unified brain theory? *Nat. Rev. Neurosci.* 11, 127–138. doi: 10.1038/nrn2787

Gehring, W. J., and Ikeo, K. (1999). Pax 6: mastering eye morphogenesis and eye evolution. *Trends Genet.* 15, 371–377. doi: 10.1016/S0168-9525(99)01776-X

Georgala, P. A., Carr, C. B., and Price, D. J. (2011). The role of Pax6 in forebrain development. *Dev. Neurobiol.* 71, 690–709. doi: 10.1002/dneu.20895

Gilbert, C. D. (1983). Microcircuitry of the visual cortex. *Ann. Rev. Neurosci.* 6, 217–247. doi: 10.1146/annurev.ne.06.030183.001245

Goddard, C. A., Sridharan, D., Huguenard, J. R., and Knudsen, E. I. (2012). Gamma oscillations are generated locally in an attention-related midbrain *Network* 73, 567–580. doi: 10.1016/j.neuron.2011.11.028

Gregoriou, G. G., Gotts, S. J., Zhou, H., and Desimone, R. (2009). High-frequency, long-range coupling between prefrontal and visual cortex during attention. *Science* 324, 1207–1210. doi: 10.1126/science.1171402

Hansen, B. J., Chelaru, M. I., and Dragoi, V. (2012). Correlated variability in laminar cortical circuits. *Neuron* 76, 590–602. doi: 10.1016/j.neuron.2012.08.029

Harris, K. D., and Shepherd, G. M. G. (2015). The neocortical circuit: themes and variations. *Nat. Neurosci.* 18, 170–181. doi: 10.1038/nn.3917

He, S., Li, Z., Ge, S., Yu, Y.-C., and Shi, S.-H. (2015). Inside-out radial migration facilitates lineage-dependent neocortical microcircuit assembly. *Neuron* 86, 1159–1166. doi: 10.1016/j.neuron.2015.05.002

Hoch, R. V., Rubenstein, J. L. R., and Pleasure, S. (2009). Genes and signaling events that establish regional patterning of the mammalian forebrain. *Semin. Cell Dev. Biol.* 20, 378–386. doi: 10.1016/j.semcdb.2009.02.005

Hubel, D. H., and Wiesel, T. N. (1977). Functional architecture of macaque monkey visual cortex. *Proc. R. Soc. Lond. B Biol. Sci.* 198, 1–59. doi: 10.1098/rspb.1977.0085

Isaacson, J. S., and Scanziani, M. (2011). How inhibition shapes cortical activity. *Neuron* 72, 231–243. doi: 10.1016/j.neuron.2011.09.027

Jia, X., Tanabe, S., and Kohn, A. (2013). Gamma and the coordination of spiking activity in early visual cortex. *Neuron* 77, 762–774. doi: 10.1016/j.neuron.2012.12.036

Karten, H. J. (1968). The ascending auditory pathway in the pigeon (Columba livia). II. Telencephalic projections of the nucleus ovoidalis thalami. *Brain Res.* 11, 134–153. doi: 10.1016/0006-8993(68)90078-4

Karten, H. J. (1969). The organization of the avian telencephalon and some speculations on the phylogeny of the amniote telencephalon. *Ann. N.Y. Acad. Sci.* 167, 164–179. doi: 10.1111/j.1749-6632.1969.tb20442.x

Karten, H. J. (1997). Evolutionary developmental biology meets the brain: the origins of mammalian cortex. *Proc. Natl. Acad. Sci. U.S.A.* 94, 2800–2804. doi: 10.1073/pnas.94.7.2800

Karten, H. J. (2013). Neocortical evolution: neuronal circuits arise independently of lamination. *Curr. Biol.* 23, R12–R15. doi: 10.1016/j.cub.2012.11.013

Kepecs, A., and Fishell, G. (2014). Interneuron cell types are fit to function. *Nature* 505, 318–326. doi: 10.1038/nature12983

Kielan-Jaworowska, Z., Cifelli, R., and Luo, Z.-X. (2004). *Mammals from the Age of Dinosaurs*. New York, NY: Columbia University Press.

Kirschfeld, K. (1992). Oscillations in the insect brain: do they correspond to the cortical gamma-waves of vertebrates? *Proc. Natl. Acad. Sci. U.S.A.* 89, 4764–4768. doi: 10.1073/pnas.89.10.4764

Kriegstein, A. R., and Connors, B. W. (1986). Cellular physiology of the turtle visual cortex: synaptic properties and intrinsic circuitry. *J. Neurosci.* 6, 178–191.

Lacalli, T. C. (2004). Sensory systems in amphioxus: a window on the ancestral chordate condition. *Brain Behav. Evol.* 64, 148–162. doi: 10.1159/000079744

Lamb, T. D. (2013). Evolution of phototransduction, vertebrate photoreceptors and retina. *Prog. Retin. Eye Res.* 36, 52–119. doi: 10.1016/j.preteyeres.2013.06.001

Lewis, C. M., Bosman, C. A., and Fries, P. (2015). Recording of brain activity across spatial scales. *Curr. Opin. Neurol.* 32, 68–77. doi: 10.1016/j.conb.2014.12.007

Li, Y., Lu, H., Cheng, P.-L., Ge, S., Xu, H., Shi, S.-H., et al. (2012). Clonally related visual cortical neurons show similar stimulus feature selectivity. *Nature* 486, 118–121. doi: 10.1038/nature11110

Lopes Da Silva, F. H., and Storm Van Leeuwen, W. (1977). The cortical source of the alpha rhythm. *Neurosci. Lett.* 6, 237–241. doi: 10.1016/0304-3940(77)90024-6

Lorente de No, R. (1938). "Architectonics and structure of the cerebral cortex," in *Physiology of the Nervous System*, ed J. F. Fulton (New York, NY: Oxford University Press), 291–330.

Lund, J. S. (1988). Anatomical organization of macaque monkey striate visual cortex. *Ann. Rev. Neurosci.* 11, 253–288. doi: 10.1146/annurev.ne.11.030188.001345

Luzzati, F. (2015). A hypothesis for the evolution of the upper layers of the neocortex through co-option of the olfactory cortex developmental program. *Front. Neurosci.* 9:162. doi: 10.3389/fnins.2015.00162

Luzzati, F., Bonfanti, L., Fasolo, A., and Peretto, P. (2009). DCX and PSA-NCAM expression identifies a population of neurons preferentially distributed in associative areas of different pallial derivatives and vertebrate species. *Cereb. Cortex* 19, 1028–1041. doi: 10.1093/cercor/bhn145

Lynch, G. (1986). *Synapses, Circuits, and the Beginnings of Memory*. Cambridge, MA: MIT Press.

Marín, G., Mpodozis, J., Sentis, E., Ossandón, T., and Letelier, J. C. (2005). Oscillatory bursts in the optic tectum of birds represent re-entrant signals from the nucleus isthmi pars parvocellularis. *J. Neurosci.* 25, 7081–7089. doi: 10.1523/JNEUROSCI.1379-05.2005

Markov, N. T., Ercsey-Ravasz, M., van Essen, D. C., Knoblauch, K., Toroczkai, Z., and Kennedy, H. (2013). Cortical high-density counterstream architectures. *Science* 342:1238406. doi: 10.1126/science.1238406

Markov, N. T., Vezoli, J., Chameau, P., Falchier, A., Quilodran, R., Huissoud, C., et al. (2014). Anatomy of hierarchy: feedforward and feedback pathways in macaque visual cortex. *J. Comp. Neurol.* 522, 225–259. doi: 10.1002/cne.23458

Medina, L., and Abellán, A. (2009). Development and evolution of the pallium. *Semin. Cell Dev. Biol.* 20, 698–711. doi: 10.1016/j.semcdb.2009.04.008

Merker, B. (2013). Cortical gamma oscillations: the functional key is activation, not cognition. *Neurosci. Biobehav. Rev.* 37, 401–417. doi: 10.1016/j.neubiorev.2013.01.013

Mitzdorf, U. (1985). Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. *Physiol. Rev.* 65, 37–100.

Mountcastle, V. B. (1997). The columnar organization of the neocortex. *Brain* 120(Pt 4), 701–722. doi: 10.1093/brain/120.4.701

Naumann, R. K., Ondracek, J. M., Reiter, S., Shein-Idelson, M., Tosches, M. A., Yamawaki, T. M., et al. (2015). The reptilian brain. *Curr. Biol.* 25, R317–R321. doi: 10.1016/j.cub.2015.02.049

Nieuwenhuys, R. (1994). The neocortex. An overview of its evolutionary development, structural organization and synaptology. *Anat. Embryol.* 190, 307–337.

Noctor, S. C., Flint, A. C., Weissman, T. A., Dammerman, R. S., and Kriegstein, A. R. (2001). Neurons derived from radial glial cells establish radial units in neocortex. *Nature* 409, 714–720. doi: 10.1038/35055553

Pinotsis, D. A., Brunet, N., Bastos, A., Bosman, C. A., Litvak, V., Fries, P., et al. (2014). Contrast gain control and horizontal interactions in V1: a DCM study. *Neuroimage* 92, 143–155. doi: 10.1016/j.neuroimage.2014.01.047

Prechtl, J. C., Bullock, T. H., and Kleinfeld, D. (2000). Direct evidence for local oscillatory current sources and intracortical phase gradients in turtle visual cortex. *Proc. Natl. Acad. Sci. U.S.A.* 97, 877–882. doi: 10.1073/pnas.97.2.877

Prechtl, J. C., Cohen, L. B., Pesaran, B., Mitra, P. P., and Kleinfeld, D. (1997). Visual stimuli induce waves of electrical activity in turtle cortex. *Proc. Natl. Acad. Sci. U.S.A.* 94, 7621–7626. doi: 10.1073/pnas.94.14.7621

Puelles, L., Kuwana, E., Puelles, E., Bulfone, A., Shimamura, K., Keleher, J., et al. (2000). Pallial and subpallial derivatives in the embryonic chick and mouse telencephalon, traced by the expression of the genes Dlx-2, Emx-1, Nkx-2.1, Pax-6, and Tbr-1. *J. Comp. Neurol.* 424, 409–438. doi: 10.1002/1096-9861(20000828)424:3%3C409::AID-CNE3%3E3.0.CO;2-7

Puelles, L., Kuwana, E., Puelles, E., and Rubenstein, J. L. (1999). Comparison of the mammalian and avian telencephalon from the perspective of gene expression data. *Eur. J. Morphol.* 37, 139–150. doi: 10.1076/ejom.37.2-3.0139

Rao, R. P., and Ballard, D. H. (1999). Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nat. Neurosci.* 2, 79–87. doi: 10.1038/4580

Ray, S., and Maunsell, J. H. R. (2015). Do gamma oscillations play a role in cerebral cortex? *Trends Cogn. Sci.* 19, 78–85. doi: 10.1016/j.tics.2014.12.002

Renart, A., de la Rocha, J., Bartho, P., Hollender, L., Parga, N., Reyes, A. et al. (2010). The asynchronous state in cortical circuits. *Science* 327, 587–590. doi: 10.1126/science.1179850

Roberts, M. J., Lowet, E., Brunet, N. M., Wal Ter, M., Tiesinga, P., Fries, P., et al. (2013). Robust gamma coherence between macaque V1 and V2 by dynamic frequency matching. *Neuron* 78, 523–536. doi: 10.1016/j.neuron.2013.03.003

Rowe, T. B., and Shepherd, G. M. (2015). The role of ortho-retronasal olfaction in mammalian cortical evolution. *J. Comp. Neurol.* doi: 10.1002/cne.23802. [Epub ahead of print].

Salazar, R. F., Dotson, N. M., Bressler, S. L., and Gray, C. M. (2012). Content-specific fronto-parietal synchronization during visual working memory. *Science* 338, 1097–1100. doi: 10.1126/science.1224000

Salinas, E., and Sejnowski, T. J. (2001). Correlated neuronal activity and the flow of neural information. *Nat. Rev. Neurosci.* 2, 539–550. doi: 10.1038/35086012

Sanes, J. R., and Zipursky, S. L. (2010). Design Principles of Insect and Vertebrate Visual Systems. *Neuron* 66, 15–36. doi: 10.1016/j.neuron.2010.01.018

Shepherd, G. M. (2011). The microcircuit concept applied to cortical evolution: from three-layer to six-layer cortex. *Front. Neuroanat.* 5:30. doi: 10.3389/fnana.2011.00030

Siegle, J. H., Pritchett, D. L., and Moore, C. I. (2014). Gamma-range synchronization of fast-spiking interneurons can enhance detection of tactile stimuli. *Nat. Neurosci.* 17, 1371–1379. doi: 10.1038/nn.3797

Silva, L. R., Amitai, Y., and Connors, B. W. (1991). Intrinsic oscillations of neocortex generated by layer 5 pyramidal neurons. *Science* 251, 432–435. doi: 10.1126/science.1824881

Singer, W. (2013). Cortical dynamics revisited. *Trends Cogn. Sci.* 17, 616–626. doi: 10.1016/j.tics.2013.09.006

Smith, G. B., Sederberg, A., Elyada, Y. M., van Hooser, S. D., Kaschube, M., and Fitzpatrick, D. (2015). The development of cortical circuits for motion discrimination. *Nat. Neurosci.* 18, 252–261. doi: 10.1038/nn.3921

Smith, L. M., Ebner, F. F., and Colonnier, M. (1980). The thalamocortical projection in Pseudemys turtles: a quantitative electron microscopic study. *J. Comp. Neurol.* 190, 445–461. doi: 10.1002/cne.901900304

Smith, M. A., Jia, X., Zandvakili, A., and Kohn, A. (2013). Laminar dependence of neuronal correlations in visual cortex. *J. Neurophysiol.* 109, 940–947. doi: 10.1152/jn.00846.2012

Spaak, E., Bonnefond, M., Maier, A., Leopold, D. A., and Jensen, O. (2012). Layer-specific entrainment of gamma-band neural activity by the alpha rhythm in monkey visual cortex. *Curr. Biol.* 22, 2313–2318. doi: 10.1016/j.cub.2012.10.020

Sridharan, D., Boahen, K., and Knudsen, E. I. (2011). Space coding by gamma oscillations in the barn owl optic tectum. *J. Neurophysiol.* 105, 2005–2017. doi: 10.1152/jn.00965.2010

Sridharan, D., and Knudsen, E. I. (2015). Gamma oscillations in the midbrain spatial attention network: linking circuits to function. *Curr. Opin. Neurol.* 31, 189–198. doi: 10.1016/j.conb.2014.11.006

Stopfer, M., Bhagavan, S., Smith, B. H., and Laurent, G. (1997). Impaired odour discrimination on desynchronization of odour-encoding neural assemblies. *Nature* 390, 70–74. doi: 10.1038/36335

Striedter, G. F. (1997). The telencephalon of tetrapods in evolution. *Brain Behav. Evol.* 49, 179–213. doi: 10.1159/000112991

Suzuki, D. G., Murakami, Y., Escriva, H., and Wada, H. (2015). A comparative examination of neural circuit and brain patterning between the lamprey and amphioxus reveals the evolutionary origin of the vertebrate visual center. *J. Comp. Neurol.* 523, 251–261. doi: 10.1002/cne.23679

Tiesinga, P. H., and Sejnowski, T. J. (2009). Cortical enlightenment: are attentional gamma oscillations driven by ING or PING? *Neuron* 63, 727–732. doi: 10.1016/j.neuron.2009.09.009

van Kerkoerle, T., Self, M. W., Dagnino, B., Gariel-Mathis, M.-A., Poort, J., van der Togt, C., et al. (2014). Alpha and gamma oscillations characterize feedback and feedforward processing in monkey visual cortex. *Proc. Natl. Acad. Sci. U.S.A.* 111, 14332–14341. doi: 10.1073/pnas.1402773111

van Vreeswijk, C., and Sompolinsky, H. (1996). Chaos in neuronal networks with balanced excitatory and inhibitory activity. *Science* 274, 1724–1726. doi: 10.1126/science.274.5293.1724

Varela, F., Lachaux, J.-P., Rodriguez, E., and Martinerie, J. (2001). The brainweb: phase synchronization and large-scale integration. *Nat. Rev. Neurosci.* 2, 229–239. doi: 10.1038/35067550

Vinck, M., Batista-Brito, R., Knoblich, U., and Cardin, J. A. (2015). Arousal and locomotion make distinct contributions to cortical activity patterns and visual encoding. *Neuron* 86, 740–754. doi: 10.1016/j.neuron.2015.03.028

von Stein, A., Chiang, C., and König, P. (2000). Top-down processing mediated by interareal synchronization. *Proc. Natl. Acad. Sci. U.S.A.* 97, 14748–14753. doi: 10.1073/pnas.97.26.14748

Wang, Y., Brzozowska-Prechtl, A., and Karten, H. J. (2010). Laminar and columnar auditory cortex in avian brain. *Proc. Natl. Acad. Sci. U.S.A.* 107, 12676–12681. doi: 10.1073/pnas.1006645107

Wilson, N. R., Runyan, C. A., Wang, F. L., and Sur, M. (2012). Division and subtraction by distinct cortical inhibitory networks *in vivo*. *Nature* 488, 343–348. doi: 10.1038/nature11347

Womelsdorf, T., Valiante, T. A., Sahin, N. T., Miller, K. J., and Tiesinga, P. H. (2014). Dynamic circuit motifs underlying rhythmic gain control, gating and integration. *Nat. Neurosci.* 17, 1031–1039. doi: 10.1038/nn.3764

Xing, D., Yeh, C.-I., Burns, S., and Shapley, R. M. (2012). Laminar analysis of visually evoked activity in the primary visual cortex. *Proc. Natl. Acad. Sci. U.S.A.* 109, 13871–13876. doi: 10.1073/pnas.1201478109

Yu, Y.-C., He, S., Chen, S., Fu, Y., Brown, K. N., Yao, X.-H., et al. (2012). Preferential electrical coupling regulates neocortical lineage-dependent microcircuit assembly. *Nature* 486, 113–117. doi: 10.1038/nature10958

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

PERSPECTIVE
published: 23 June 2015
doi: 10.3389/fnins.2015.00223

On the hodological criterion for homology

Macarena Faunes[1]*, *João Francisco Botelho*[1,2], *Patricio Ahumada Galleguillos*[3] and *Jorge Mpodozis*[4]

[1] Department of Anatomy, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand, [2] Grupo Fritz Müller-Desterro de Estudos em Filosofia e História da Biologia, Departamento de Filosofia, Universidade Federal de Santa Catarina, Florianópolis, Brasil, [3] Programa de Anatomía y Biología del Desarrollo, Facultad de Medicina, Instituto de Ciencias Biomédicas, Universidad de Chile, Santiago, Chile, [4] Laboratorio de Neurobiología y Biología del Conocer, Departamento de Biología, Facultad de Ciencias, Universidad de Chile, Santiago, Chile

Owen's pre-evolutionary definition of a homolog as "the same organ in different animals under every variety of form and function" and its redefinition after Darwin as "the same trait in different lineages due to common ancestry" entail the same heuristic problem: how to establish "sameness." Although different criteria for homology often conflict, there is currently a generalized acceptance of gene expression as the best criterion. This gene-centered view of homology results from a reductionist and preformationist concept of living beings. Here, we adopt an alternative organismic-epigenetic viewpoint, and conceive living beings as systems whose identity is given by the dynamic interactions between their components at their multiple levels of composition. We posit that there cannot be an absolute homology criterion, and instead, homology should be inferred from comparisons at the levels and developmental stages where the delimitation of the compared trait lies. In this line, we argue that neural connectivity, i.e., the hodological criterion, should prevail in the determination of homologies between brain supra-cellular structures, such as the vertebrate pallium.

Keywords: amniote pallium, amygdala, cortex, dorsal ventricular ridge, epigenesis, evolution, organization

OPEN ACCESS

Edited by:
J. Michael Williams, Drexel University, USA

Reviewed by:
Monica Truelove-Hill, Drexel University, USA
Matjaz Kuntner, Scientific Research Centre of the Slovenian Academy of Sciences and Arts, Slovenia

***Correspondence:**
Macarena Faunes, Department of Anatomy, Faculty of Medical and Health Sciences, University of Auckland, Building 502, 85 Park Road, Auckland 1023, New Zealand
macare.fc@gmail.com

Specialty section:
This article was submitted to Evolutionary Psychology and Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *29 March 2015*
Accepted: *08 June 2015*
Published: *23 June 2015*

Citation:
Faunes M, Francisco Botelho J, Ahumada Galleguillos P and Mpodozis J (2015) On the hodological criterion for homology. Front. Neurosci. 9:223. doi: 10.3389/fnins.2015.00223

Introduction: The Problem of Homology

The concept of homology has long been implicitly used by biologists, as comparison has been the basis of our classification of the natural world at least since Aristotle (Russell, 1916; Nordenskiold, 1928). Nevertheless, the study of structural correspondence moved to the foreground (Russell, 1916; Coleman, 1971) in the first half of the nineteenth century, when biology emerged as an independent science and morphology became its core discipline. By comparing the structure of living beings, early morphologists sought the laws that govern form and function. Similar structures meant similar plans (*Gestalt*) or similar generational rules (*Bildung*), and the comparison of anatomy and embryology were a means to discover them. Therefore, biological similarity was explained by sameness of type, much like similar structures in minerals. In this typological context, Richard Owen defined a "homolog" as "the same organ in different animals under every variety of form and function" (Owen, 1843; Panchen, 1994).

Biology was radically transformed at the second half of the nineteenth century by the theory of evolution (Ruse, 1999; Bowler, 2003). The large amount of data gathered from comparative anatomy and embryology by earlier morphologists was one of the most important sets of evidence presented by Darwin (1859) to support his theory, and it was subsequently re-interpreted in light of

the new theoretical framework. The archetype of early morphologists was replaced by the ancestor, and the concept of homology was reappraised in genealogical terms (Haeckel, 1874). As stated by Karl Gegenbaur, a leading morphologist converted to evolutionism, "the theory allowed what previously had been designated as *Bauplan* or *Typus* to appear as the sum of structural elements of animal organization which are propagated by means of inheritance" (cited in Coleman, 1976). The explanation for sameness changed from shared organizational rules to shared genealogy, and the "homolog" became defined as "the same trait in different lineages due to common ancestry" (Lankester, 1870).

Although typological and genealogical concepts of homology entailed different views of *sameness,* from a practical point of view, both concepts involved the same operational criteria to define it (Wagner, 1994; Bolker and Raff, 1996; Griffiths, 2007; Hall, 2007). In both cases, homologies could only be inferred by comparing features of the ontogeny and/or the structure of the trait among organisms. However, comparisons of different features, i.e., the use of different homology criteria, often conflict with each other. The rise of experimental embryology at the end of the nineteenth century, and the following advances in cell biology and classical genetics, nourished the expectation that the discovery of developmental mechanisms shared by different lineages would yield an absolute biological criterion for homology. Yet, the many advances in embryology and genetics failed to achieve this. The lack of a unified criterion has persisted obstinately since the origins of evolutionary biology (Darwin, 1859, p. 532) and cell biology (Wilson, 1894), and was thoroughly exposed by De Beer (1971) in his classic paper entitled "Homology: an unsolved problem". The main conclusions drawn by de Beer were:

(i) *"…correspondence between homologous structures cannot be pressed back to similarity of position of the cells of the embryo or the parts of the egg out of which these structures are ultimately differentiated."*

(ii) *"…homologous structures can owe their origin and stimulus to differentiate to different organizer-induction processes without forfeiting their homology."*

(iii) *"…characters controlled by identical genes are not necessarily homologous."*

(iv) *"…homologous structures need not be controlled by identical genes, and homology of phenotypes does not imply similarity of genotypes."*

The problem of *which homology criteria to choose* is perhaps particularly complicated in the field of neuroscience. The structural complexity of the nervous system and its interactions with sensory and motor organs offer multiple possible criteria, and in more than a few instances different criteria disagree (Campbell and Hodos, 1970). This means that anatomical, embryological, physiological, and behavioral features are not always conserved together. For example, in different animals, neurons can have similar connectivity (or *hodology*), neurochemistry and function but display different morphologies and ion channel densities (e.g., Purves and Lichtman, 1985; Marder and Goaillard, 2006) or develop from different embryonic precursors (e.g., Glover, 2001). In the same way, similar behaviors can be conserved despite changes in the underlying neural circuits (e.g., Newcomb et al., 2012).

Even though de Beer's problem remains unsolved (see for example Weiss and Fullerton, 2000; True and Haag, 2001; Kawasaki et al., 2005; Schierenberg, 2005), there is currently an assumption—implicit or explicit—that homology problems must be addressed by developmental genetics. Many recent events, such as the appearance of DNA sequencing tools, the concept of regulatory genes in eukaryotes and the *in situ* analysis of genetic expression, converged to renew the hopes of finding an absolute criterion for homology. Indeed, comparative developmental genetics has produced some of the most important achievements in evolutionary biology in the last decades, resulting in profound consequences to the concept of homology.

Saint-Hilaire's Lobster and the Dorsoventral Patterning Genes: The Reductionist Appraisal of an Organismic Statement

A good example reflecting the historical implications of the developmental genetics approach is the 1990s revival of Geoffroy Saint-Hilaire's hypothesis of the morphological homology between the dorsal side of vertebrates and the ventral side of arthropods. Around 30 years before Owen articulated his definition of homology, the pre-evolutionary anatomist Geoffroy Saint-Hilaire was already seeking a formal criterion for designating homologs (which he called "analogs"). In the preliminary discourse of the first tome of his "Philosophie Anatomique" he offers the following criterion: "The only generality to be applied to the species is given by the position, the relations and dependences between the parts, that is, by what I embrace and designate as connections" (Saint-Hilaire, 1818). By proposing a unity of composition, or "*unité de système dans la composition et l'arrangement des parties organiques*" ("unity of system in the composition and arrangement of organic parts") for all animals, Saint Hilaire defied the ruling notion of the time, put forward by his colleague Georges Cuvier. According to Cuvier, every animal followed the body plan of one of the four *embranchements* of the animal kingdom: *vertebrata, mollusca, articulata, and radiata* (Cuvier et al., 1817). With his *loi des connections* (law of connections), according to which the connections held between homologous organs in different animals remain constant, Saint-Hilaire established various homologies between vertebrates and invertebrates, which resulted in the indignation of Cuvier. One of his audacious proposals was that the body plan of a lobster, an *articulata*, was the same as that of a *vertebrata*, only with its dorsoventral axis inverted (Saint-Hilaire, 1998 [1822]). This lead to a great controversy that most historians agree was won by Cuvier.

Molecular embryologists reappraised Saint-Hilarie's hypothesis based on the inverted similarity of genes expressed in the dorsal and ventral sides of the embryos of fruit flies and frogs (Arendt and Nubler-Jung, 1994; de Robertis and Sasai, 1996). The finding of a conserved set of molecular interactions led them to postulate the inversion of the dorsoventral axis

during early chordates evolution and therefore to recognize the homology between vertebrate and arthropod nervous and digestive systems. The fact that Saint Hilaire's hypothesis—edified on the basis of comparative anatomy—only came to be reconsidered after more than 150 years, following findings in the field of molecular biology illustrates the impact of the developmental/genetic criteria of homology in current biology. The discovery of common DNA sequences and molecular interactions across animal phyla revealed an unexpected new level of conservation. A number of evolutionary developmental biologists took these and other similar findings with caution and postulated the term "deep homology" to refer to the conservation of a "genetic regulatory apparatus" in morphologically disparate traits among distantly related species (Shubin et al., 1997; Hall, 2003). However, many others took those cases as exemplars for a new reductionist agenda: to elucidate the conservation of molecular processes in early ontogeny in order to resolve problematic homologies.

Nevertheless, considering the difficulties faced by developmental criteria when determining homology, we could pose two counterfactual questions: Could we confidently ascertain that the neural system of arthropods and vertebrates are non-homologs if they had different molecular mechanisms of dorso-ventral axis specification? Certainly not, since variations in developmental mechanisms at early ontogenetic stages occur remarkably often. Inversely, could we confidently ascertain as homologs any neural and digestive systems that are specified by the same early developmental mechanism? Neither, since common developmental mechanisms can generate different structures.

A Competing Organismic-epigenetic View of Homology

Why does developmental genetics face such hindrances when attempting to provide an absolute criterion for homology? We believe this to be the consequence of one of the most prominent characteristics of living beings: they are dynamic systems organized into multiple levels (Jacob, 1970; Mayr, 1982). The hegemony usually granted to developmental and gene expression-centered homology criteria results from ontological assumptions that collapse the levels of organization and the embryological history of organisms into their lower levels and first stages of development. These assumptions are the consequence of a reductionist and preformationist view of living beings according to which development consists of the execution of a genetically-coded building program. Organisms are regarded in this framework as mosaics of ontogenetically independent components whose structural properties are determined not through their mutual interactions during development, but by the accomplishment of their corresponding segment of the genetic program (Carroll, 2005; Hoekstra and Coyne, 2007). If this were the case, then the identity of a trait would be solely given by gene expression patterns during its development.

If we assume that living beings are dynamically changing systems that exist through continuous interactions between their components in the epigenetic course of development, then we cannot reduce the identity of all traits to a particular ontogenetic stage, such as early development, or a particular level of organization, such as the molecular level. The components of a living system can (and constantly do) change without the identity of the system nor the coherence with its environment being lost, and these changes can occur at some levels of its organization without producing changes in other levels, during both ontogeny and phylogeny (Bertalanffy, 1962; Maturana and Varela, 1973; Maturana and Mpodozis, 2000)[1]. It is the continuous historical (moment to moment) realization of their organization—i.e., of the relations held between their organic components at different structural levels—what confers to organisms their identity at any stage of ontogeny.

Three relevant consequences follow the adoption of this organismic/epigenetic approach to living beings:

(i) Neither developmental nor genetic comparisons can supply an absolute criterion for determining homology. Given the systemic nature of living organisms and the epigenetic nature of their development, the recurrence of traits between generations does not imply the recurrence of genetic nor developmental processes, because a given ontogenetic state can be constituted by different sets of components and attained by different developmental trajectories.

(ii) When establishing a homology, both the level of organization and the ontogenetic stage to be considered must be in agreement with the delimitation of the compared trait. Inasmuch as there is no privileged level or stage in the realization of living organization, delimiting the object is part of the establishment of a homology. The delimitation of a trait is the distinction of a particular organization, a particular set of relations held between components within the organism, and therefore it is defined by the observer and is not intrinsic to the composition of the living system (Wimsatt, 1972; Striedter, 1999; Griesemer, 2000; Winther, 2006). In the same way, the establishment of a homology is defined by the observer because it is the distinction of the same set of relations within two individuals or lineages (Maturana, 2002). The more reliable criteria to assess a homology will be those aspects of the compared trait that are most structurally restricted to change while the organization that defines the trait is conserved.

(iii) The phylogenetic explanation is independent of the establishment of a homology (Amundson and Lauder, 1994). Considering that inheritance is the repetition of a process and not the transmission of a trait (Maturana and Mpodozis, 2000; Oyama et al., 2001), whether a homologous trait is present in the most recent common ancestor of the compared species (what has been called a "true" homology)

[1]The evolution of actin filaments is a good example. The DNA sequences used by the cell to the production of actin proteins in eukaryotes are so different from the sequences used to produce MreB in bacteria that their homology had been ignored until the tertiary structures of the proteins were revealed, showing that lower levels of organization have changed while the structure necessary for the process of dynamical polymerization has been conserved (Erickson, 2001; Colavin et al., 2014).

or is the result of parallel evolution ("latent" homology) is relevant for its explanation, but irrelevant for its definition (Arendt and Reznick, 2008). In both cases the homology results from the recurrence of a historical, epigenetic process[2].

A Long-standing Homology Problem in the Nervous System: The Case of the Amniote Telencephalon

The pallium is the dorsal part of the vertebrate telenchephalon, and in mammals its most prominent structure is the six-layered isocortex. In diapsids (reptiles and birds), however, most of the pallium is composed of the *dorsal ventricular ridge* (DVR), which is organized into nuclei. Homologies between the pallia of amniotes have been subject of much debate over the last 20 years. The controversy has been previously reviewed by others (e.g., Reiner et al., 2005) and will be presented here only briefly. The first tract-tracing studies that began to reveal the organization of the sensory collothalamic projections (i.e., those sensory projections reaching the thalamus through a relay in the midbrain) to the avian DVR led to the proposal of a possible homology between nuclei in the avian anterior DVR and specific layers in mammalian temporal isocortices (Karten, 1969). Further studies continued to reinforce this notion by showing striking similarities in the overall organization of sensorimotor circuits; from the midbrain and thalamic structures (which become homologized by extension, e.g., Major et al., 2000) to the intra DVR circuits and the targets of their descending projections (e.g., Wild et al., 1993; Wang et al., 2010; Ahumada et al., 2015).

Twenty-five years after it was first enunciated, this "isocortex/DVR hypothesis" was challenged by the proposal of the "claustroamygdala/DVR hypothesis." First, based mostly on work on the connections of the reptile forebrain, Bruce and Neary (1995) put forward the hypothesis that the mammalian homolog of the DVR was the basolateral amygdala (**Figure 1**). Even though this hypothesis has received some further support from hodological evidence (e.g., Novejarque et al., 2004; Guirado et al., 2005), what truly fueled the debate was the later work on homeobox gene expression patterns during development (Reiner et al., 2005; Bruce, 2012). Different authors proposed the amygdala and/or claustrum and endopiriform nucleus as mammalian homologs to the DVR (Striedter, 1997; Fernández et al., 1998; Puelles et al., 2000; Aboitiz et al., 2003). Thus, the earlier isocortex vs. claustroamygdala controversy became a debate between hodology and development/gene expression. More recently, this debate has moved to a new phase, primarily due to novel evidence showing that specific components of the avian DVR express layer-specific isocortical markers (Dugas-Ford et al., 2012; Chen et al., 2013; Suzuki and Hirata, 2013) and that there is a common pattern of gene-expression between the DVR and the hyperpallium (the widely-accepted diapsid homolog to the striate cortex, see **Figure 1B**) during development (Jarvis et al., 2013). These new data are seen as key support to the isocortex hypothesis (Karten, 2013; Reiner, 2013), and thus –much like the case of Saint Hilaire's Lobster– the focus of the debate has shifted to development/gene expression grounds.

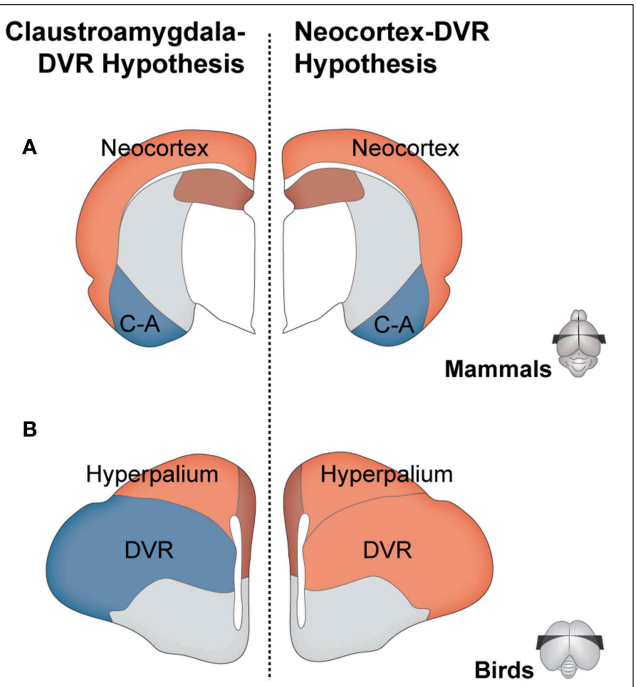


FIGURE 1 | Competing hypotheses regarding the homologies between mammalian and diapsid pallia. Schematic representation of coronal sections of the brains of a mammal **(A)** and a bird (**B**, as example of a diapsid). According to the claustroamygdala-DVR hypothesis (left side), the avian DVR and hyperpallium are homologous to the mammalian claustroamygdalar complex (blue), and neocortex (light red), respectively. According to the isocortex-DVR hypothesis (right side), the avian DVR and hyperpallium are both homologous to the mammalian isocortex (light red).

We consider the reduction of the problem to a case of development/gene expression similarities to be intrinsically misdirected. Whatever their embryonic or adult patterns of gene expression, the hodological similarities of the diapsid DVR with the mammalian isocortex and basolateral amygdala remain the same. Homologies of gene-expression or cell types do not imply homologies of the supra-cellular structures containing them, and homologies of embryonic domains of gene expression certainly do not imply homologies of the resulting adult structures. Levels and stages of comparison should not be intermingled.

Accordingly, we think that the question about the identity of the adult diapsid DVR can only be focused at the level where the traits "neocortex" and "amygdala" are defined, which is the supra-neuronal level. What defines the identity of a supraneuronal structure is the set of relations it holds with the rest of the nervous system, which in an adult nervous system conform sensorimotor correlations of neural activity. The sensorimotor correlations that define the neocortex and amygdala are attained by the functional

[2]De Beer (1971) and Hall (2007) have also proposed a congruency between "true" and "latent" homologies, but their analyses differ to and have points of disagreement with ours, as they appeal to the phylogenetic continuity of the "developmental basis" (i.e., developmental genes) for parallel evolution to produce "true" homologous structures.

interconnectivity between different neuronal groups and sensory and motor organs, and not by properties intrinsic to any of them. The aspects more restricted to change, and thus the most useful as homology criteria, are those directly related to the connectivity that maintain these sensorimotor correlations. These can include neuronal morphology, neurochemistry, and most importantly, hodology. Therefore, we consider that the way to settle the issue of the diapsid DVR is to further unveil the organization of the circuits it is involved in.

Conclusions

Most contemporaneous philosophers of science accepted the assumption that scientific concepts should be dealt with in their social and historical context (Dupré, 2012)[3]. To recognize that scientific concepts are determined by the operations and practices employed to define them, and not by the intrinsic properties of the object, is an important premise in the present debate about the definition of homology. To search for an absolute or "biological" criterion of homology, able to explain sameness across time and levels, is unfeasible and unnecessary. The sound establishment of a homology means the sound comparison and description of sameness in a scientific domain. Like a sound experiment, it shall survive to different theories or explanations (Griffiths, 2007). In other words, whatever our explanation for homology is, it will not deny the sameness in the connectivity of the vertebrate visual system described by Cajal, the ontogeny of the mandibular arches described by Meckel, or the synteny of genes described by genomics studies.

The acknowledgement of the organismic-epigenetic nature of living beings accounts for the incongruences in the search for an absolute homology criterion and for the necessity to consider the ontogenetic and organizational delimitation of the compared trait when attempting to establish a homology. Homologies are not to be determined according to the fulfillment of a unique criterion, nor the largest amount of criteria, but of the most appropriate criteria according to the level of analysis where the identity of the trait is defined. From this organismic-epigenetic perspective, the identity of the adult nervous system, when considered from a high level of its organization, is defined by the interactions that allow the coordination of the activity of different neuronal populations and motor and sensory systems, i.e., its functional connectivity. Focusing on the hodological criterion rescues a key aspect of living beings: that they are processes. As such, the identities of their components are given by their interactions with the rest of the organism during the process of life, or what Saint-Hilaire called *connections*.

[3]The epistemology of the concepts of *gene* and *species* illustrates well the power of this new kind of philosophical analysis in biological sciences. *Species* and *genes* mean different things for different sets of scientists and several philosophers of biology tend to assume that they are defined and transformed by the practice (Dupré, 2012; Godfrey-Smith, 2013; Griffiths and Stotz, 2013).

Acknowledgments

We thank Alfonso Deichler for giving us feedback on previous versions of this manuscript, Laura Fenlon, Rashi Karunasinghe, Jérôme Plumat, and Gabriel Renié for their valuable editorial help, and Magno Rompiato for being a source of inspiration. This work was supported by FONDECYT 1120124 to JM.

References

Aboitiz, F., Morales, D., and Montiel, J. (2003). The evolutionary origin of the mammalian isocortex: towards an integrated developmental and functional approach. *Behav. Brain Sci.* 26, 535–552. doi: 10.1017/S0140525X03000128

Ahumada, P., Fernandez, M., Marin, G. J., Letelier, J. C., and Mpodozis, J. (2015). Anatomical organization of the visual dorsal ventricular ridge in the chick (*Gallus gallus*): layers and columns in the avian pallium. *J. Comp. Neurol.* doi: 10.1002/cne.23808. [Epub ahead of print].

Amundson, R., and Lauder, G. V. (1994). Function without purpose. *Biol. Philos.* 9, 443–469. doi: 10.1007/BF00850375

Arendt, D., and Nubler-Jung, K. (1994). Inversion of dorsoventral axis? *Nature* 371, 26–26. doi: 10.1038/371026a0

Arendt, J., and Reznick, D. (2008). Convergence and parallelism reconsidered: what have we learned about the genetics of adaptation? *Trends Ecol. Evol.* 23, 26–32. doi: 10.1016/j.tree.2007.09.011

Bertalanffy, L. (1962). *Modern Theories of Development: An Introduction to Theoretical Biology*. New York, NY: Harper Torchbooks.

Bolker, J. A., and Raff, R. A. (1996). Developmental genetics and traditional homology. *Bioessays* 18, 489–494. doi: 10.1002/bies.950180611

Bowler, P. J. (2003). *Evolution: The History of an Idea.* Berkeley: University of California Press.

Bruce, L. L. (2012). The puzzle of forebrain evolution. *Brain Behav. Evol.* 79, 141. doi: 10.1159/000335343

Bruce, L. L., and Neary, T. J. (1995). The limbic system of tetrapods: a comparative analysis of cortical and amygdalar populations. *Brain Behav. Evol.* 46, 224–234. doi: 10.1159/000113276

Campbell, C. B. G., and Hodos, W. (1970). The concept of homology and the evolution of the nervous system. *Brain Behav. Evol.* 3, 353–367. doi: 10.1159/000125482

Carroll, S. B. (2005). *Endless Forms Most Beautiful: The New Science of Evo Devo and the Making of the Animal Kingdom*. New York, NY: WW Norton & Company.

Chen, C. C., Winkler, C. M., Pfenning, A. R., and Jarvis, E. D. (2013). Molecular profiling of the developing avian telencephalon: regional timing and brain subdivision continuities. *J. Comp. Neurol.* 521, 3666–3701. doi: 10.1002/cne.23406

Colavin, A., Hsin, J., and Huang, K. C. (2014). Effects of polymerization and nucleotide identity on the conformational dynamics of the bacterial actin homolog MreB. *Proc. Natl. Acad. Sci. U.S.A.* 111, 3585–3590. doi: 10.1073/pnas.1317061111

Coleman, W. (1971). *Biology in the Nineteenth Century: Problems of Form, Function and Transformation*. Cambridge: Cambridge University Press.

Coleman, W. (1976). Morphology between type concept and descent theory. *J. Hist. Med. Allied Sci.* 31, 149–175. doi: 10.1093/jhmas/XXXI.2.149

Cuvier, G., Latreille, P. A., Laurillard, C. L., Louvet, G. P., and Pierron, J. A. (1817). *Le Règne Animal Distribué D'après son Organisation: Pour Servir de Base a L'histoire Naturelle des Animaux et D'introduction a L'anatomie Comparée/par M. le Cher. Cuvier; Avec Figures, Dessinées D'après nature*. Paris: Déterville.

Darwin, C. R. (1859). *The Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*. London: John Murray.

De Beer, G. R. (1971). *Homology; An Unsolved Problem.* London: Oxford University Press.

de Robertis, E. M., and Sasai, Y. (1996). A common plan for dorsoventral patterning in Bilateria. *Nature* 380, 37–40. doi: 10.1038/380037a0

Dugas-Ford, J., Rowell, J. J., and Ragsdale, C. W. (2012). Cell-type homologies and the origins of the neocortex. *Proc. Natl. Acad. Sci. U.S.A.* 109, 16974–16979. doi: 10.1073/pnas.1204773109

Dupré, J. (2012). *Processes of Life: Essays in the Philosophy of Biology*. Oxford: Oxford University Press.

Erickson, H. P. (2001). Cytoskeleton: evolution in bacteria. *Nature* 413, 30–30. doi: 10.1038/35092655

Fernández, A. S., Pieau, C., Repérant, J., Boncinelli, E., and Wassef, M. (1998). Expression of the Emx-1 and Dlx-1 homeobox genes define three molecularly distinct domains in the telencephalon of mouse, chick, turtle and frog embryos: implications for the evolution of telencephalic subdivisions in amniotes. *Development* 125, 2099–2111.

Glover, J. C. (2001). Correlated patterns of neuron differentiation and Hox gene expression in the hindbrain: a comparative analysis. *Brain Res. Bull.* 55, 683–693. doi: 10.1016/S0361-9230(01)00562-7

Godfrey-Smith, P. (2013). *Philosophy of Biology*. Princeton, NJ: Princeton University Press.

Griesemer, J. (2000). "Reproduction and the reduction of genetics," in *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives*, eds P. J. Beurton, R. Falk, and H.-J. Rheinberger (Cambridge: Cambridge University Press), 240–285.

Griffiths, P. E. (2007). The phenomena of homology. *Biol. Philos.* 22, 643–658. doi: 10.1007/s10539-007-9090-x

Griffiths, P., and Stotz, K. (2013). *Genetics and Philosophy: An Introduction*. Cambridge: Cambridge University Press.

Guirado, S., Real, M. A., and Dávila, J. C. (2005). The ascending tectofugal visual system in amniotes: new insights. *Brain Res. Bull.* 66, 290–296. doi: 10.1016/j.brainresbull.2005.02.015

Haeckel, E. (1874). Memoirs: the Gastraea-Theory, the phylogenetic classification of the animal kingdom and the homology of the germ-lamellæ. *Q. J. Microsc. Sci.* 2, 142–165.

Hall, B. K. (2003). Descent with modification: the unity underlying homology and homoplasy as seen through an analysis of development and evolution. *Biol. Rev.* 78, 409–433. doi: 10.1017/S1464793102006097

Hall, B. K. (2007). Homoplasy and homology: dichotomy or continuum? *J. Hum. Evol.* 52, 473–479. doi: 10.1016/j.jhevol.2006.11.010

Hoekstra, H. E., and Coyne, J. A. (2007). The locus of evolution: evo devo and the genetics of adaptation. *Evolution* 61, 995–1016. doi: 10.1111/j.1558-5646.2007.00105.x

Jacob, F. (1970). *La Logique du Vivant: Une Histoire de L'hérédité*. Paris: Gallimard.

Jarvis, E. D., Yu, J., Rivas, M. V., Horita, H., Feenders, G., Whitney, O., et al. (2013). Global view of the functional molecular organization of the avian cerebrum: mirror images and functional columns. *J. Comp. Neurol.* 521, 3614–3665. doi: 10.1002/cne.23404

Karten, H. J. (1969). The organization of the avian telencephalon and some speculations on the phylogeny of the amniote telencephalon. *Ann. NY. Acad. Sci.* 167, 164–179. doi: 10.1111/j.1749-6632.1969.tb20442.x

Karten, H. J. (2013). Neocortical evolution: neuronal circuits arise independently of lamination. *Curr. Biol.* 23, R12–R15. doi: 10.1016/j.cub.2012.11.013

Kawasaki, K., Suzuki, T., and Weiss, K. M. (2005). Phenogenetic drift in evolution: the changing genetic basis of vertebrate teeth. *Proc. Natl. Acad. Sci. U.S.A.* 102, 18063–18068. doi: 10.1073/pnas.0509263102

Lankester, E. R. (1870). II.—On the use of the term homology in modern zoology, and the distinction between homogenetic and homoplastic agreements. *Ann. Mag. Nat. Hist.* 6, 34–43. doi: 10.1080/00222937008696201

Major, D. E., Luksch, H., and Karten, H. J. (2000). Bottlebrush dendritic endings and large dendritic fields: motion-detecting neurons in the mammalian tectum. *J. Comp. Neurol.* 423, 243–260. doi: 10.1002/1096-9861(20000724)423:2<243::AID-CNE5>3.0.CO;2-5

Marder, E., and Goaillard, J. M. (2006). Variability, compensation and homeostasis in neuron and network function. *Nat. Rev. Neurosci.* 7, 563–574. doi: 10.1038/nrn1949

Maturana, H. (2002). Autopoiesis, structural coupling and cognition: a history of these and other notions in the biology of cognition. *Cybern. Hum. Know.* 9, 5–34.

Maturana, H., and Mpodozis, J. (2000). The origin of species by means of natural drift El origen de las especies por medio de la deriva natural. *R. Chilena Hist. Nat.* 73, 261–310. doi: 10.4067/S0716-078X2000000200005

Maturana, H. R., and Varela, F. G. (1973). *De Máquinas y Seres Vivos*. Santiago: Editorial Universitaria.

Mayr, E. (1982). *The Growth of Biological Thought*. Cambridge: Harvard University Press.

Newcomb, J. M., Sakurai, A., Lillvis, J. L., Gunaratne, C. A., and Katz, P. S. (2012). Homology and homoplasy of swimming behaviors and neural circuits in the Nudipleura (Mollusca, Gastropoda, Opisthobranchia). *Proc. Natl. Acad. Sci. U.S.A.* 109, 10669–10676. doi: 10.1073/pnas.1201877109

Nordenskiold, E. (1928). *The History of Biology: A Survey*. New York, NY: Tudor Publishing.

Novejarque, A., Lanuza, E., and Martínez−García, F. (2004). Amygdalostriatal projections in reptiles: a tract−tracing study in the lizard *Podarcis hispanica*. *J. Comp. Neurol.* 479, 287–308. doi: 10.1002/cne.20309

Owen, R. (1843). *Lectures on the Comparative Anatomy and Physiology of the Vertebrate Animals: Delivered at the Royal College of Surgeons of England in 1843*. London: Longman, Brown, Green, and Longmans.

Oyama, S., Griffiths, P., and Gray, D. (2001). *Cycles of Contingencies: Developmental Systems and Evolution*. Cambridge: MIT Press.

Panchen, A. L. (1994). "Richard Owen and the concept of homology," in *Homology: The Hierarchical Basis of Comparative Biology*, ed B. K. Hall (San Diego, CA: Academic Press), 21–62.

Puelles, L., Kuwana, E., Puelles, E., Bulfone, A., Shimamura, K., Keleher, J., et al. (2000). Pallial and subpallial derivatives in the embryonic chick and mouse telencephalon, traced by the expression of the genes Dlx2, Emx1, Nkx2.1, Pax6, and Tbr1. *J. Comp. Neurol.* 424, 409–438. doi: 10.1002/1096-9861(20000828)424:3<409::AID-CNE3>3.0.CO;2-7

Purves, D., and Lichtman, J. W. (1985). Geometrical differences among homologous neurons in mammals. *Science* 228, 298–302. doi: 10.1126/science.3983631

Reiner, A. (2013). You are who you talk with-a commentary on Dugas-Ford et al. PNAS, 2012. *Brain Behav. Evol.* 81, 146–149. doi: 10.1159/000348281

Reiner, A., Yamamoto, K., and Karten, H. J. (2005). Organization and evolution of the avian forebrain. *Anat. Rec. A Discov. Mol. Cell. Evol. Biol.* 287, 1080–1102. doi: 10.1002/ar.a.20253

Ruse, M. (1999). *The Darwinian Revolution: Science Red in Tooth and Claw*. Chicago, IL: University of Chicago Press.

Russell, E. S. (1916). *Form and Function: A Contribution to the History of Animal Morphology*. London: John Murray.

Saint-Hilaire, G. (1818). *Philosophie Anatomique. Tome Premier. Des Organes Respiratoires Sous le Rapport de la Détermination et de L'identité de Leur Pièces Osseuses*. Paris: J.B. Baillière.

Saint-Hilaire, G. (1998 [1822]). "Considérations générales sur la vertèbre," in *Étienne Geoffroy Saint-Hilaire. Un Naturaliste Visionnaire*, ed H. L. Guyader (Paris: Belin), 80–105.

Schierenberg, E. (2005). Unusual cleavage and gastrulation in a freshwater nematode: developmental and phylogenetic implications. *Dev. Genes Evol.* 215, 103–108. doi: 10.1007/s00427-004-0454-9

Shubin, N., Tabin, C., and Carroll, S. (1997). Fossils, genes and the evolution of animal limbs. *Nature* 388, 639–648. doi: 10.1038/41710

Striedter, G. F. (1997). The telencephalon of tetrapods in evolution. *Brain Behav. Evol.* 49, 179–194. doi: 10.1159/000112991

Striedter, G. F. (1999). "Homology in the nervous system: of characters, embryology and levels of analysis," in *Homology (Novartis Foundation Symposium 222)*, ed B. K. Hall (Chichester: John Wiley & Sons), 158–169.

Suzuki, I. K., and Hirata, T. (2013). Neocortical neurogenesis is not really "neo": a new evolutionary model derived from a comparative study of chick pallial development. *Dev. Growth Differ.* 55, 173–187. doi: 10.1111/dgd.12020

True, J. R., and Haag, E. S. (2001). Developmental system drift and flexibility in evolutionary trajectories. *Evol. Dev.* 3, 109–119. doi: 10.1046/j.1525-142x.2001.003002109.x

Wagner, G. P. (1994). "Homology and the mechanisms of development," in *Homology: The Hierarchical Basis of Comparative Biology*, ed B. K. Hall (San Diego, CA: Academic Press), 273–299. doi: 10.1016/B978-0-08-057430-1.50014-7

Wang, Y., Brzozowska-Prechtl, A., and Karten, H. J. (2010). Laminar and columnar auditory cortex in avian brain. *Proc. Natl. Acad. Sci. U.S.A.* 107, 12676–12681. doi: 10.1073/pnas.1006645107

Weiss, K. M., and Fullerton, S. M. (2000). Phenogenetic drift and the evolution of genotype–phenotype relationships. *Theor. Popul. Biol.* 57, 187–195. doi: 10.1006/tpbi.2000.1460

Wild, J. M., Karten, H. J., and Frost, B. J. (1993). Connections of the auditory forebrain in the pigeon (*Columba livia*). *J. Comp. Neurol.* 337, 32–62. doi: 10.1002/cne.903370103

Wilson, E. B. (1894). "Embryological criterion of homology," in *Biological Lectures Delivered at the Marine Biological Laboratory of Wood's Holl* (Boston, MA: Ginn & Co), 101–124.

Wimsatt, W. C. (1972). "Complexity and organization," in *PSA 1972*, eds K. F. Schaffner and R. S. Cohen (Dordrecht: D. Reidel Publishing Co.), 67–86.

Winther, R. G. (2006). Parts and theories in compositional biology. *Biol. Philos.* 21, 471–499. doi: 10.1007/s10539-005-9002-x

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

HYPOTHESIS AND THEORY
published: 14 October 2015
doi: 10.3389/fnins.2015.00377

Pallial patterning and the origin of the isocortex

Juan F. Montiel[1,2]* *and Francisco Aboitiz*[3]

[1] *Facultad de Medicina, Centro de Investigación Biomédica, Universidad Diego Portales, Santiago, Chile,* [2] *Medical Research Council Functional Genomics Unit, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK,* [3] *Departamento de Psiquiatría, Escuela de Medicina, and Centro Interdisciplinario de Neurociencia, Pontificia Universidad Católica de Chile, Santiago, Chile*

Together with a complex variety of behavioral, physiological, morphological, and neurobiological innovations, mammals are characterized by the development of an extensive isocortex (also called neocortex) that is both laminated and radially organized, as opposed to the brain of birds and reptiles. In this article, we will advance a developmental hypothesis in which the mechanisms of evolutionary brain growth remain partly conserved across amniotes (mammals, reptiles and birds), all based on Pax6 signaling or related morphogens. Despite this conservatism, only in mammals there is an additional upregulation of dorsal and anterior signaling centers (the cortical hem and the anterior forebrain, respectively) that promoted a laminar and a columnar structure into the neocortex. It is possible that independently, some birds also developed an upregulated dorsal pallium.

Keywords: isocortical development, Pax6, Wnt, antihem, hem

OPEN ACCESS

Edited by:
Lisa M. Renzi,
The University of Georgia, USA

Reviewed by:
Luca Bonfanti,
University of Turin, Italy
Federico Luzzati,
University of Turin, Italy

***Correspondence:**
Juan F. Montiel
juan.montiel@udp.cl

Specialty section:
This article was submitted to Evolutionary Psychology and Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *13 July 2015*
Accepted: *28 September 2015*
Published: *14 October 2015*

Citation:
Montiel JF and Aboitiz F (2015) Pallial patterning and the origin of the isocortex. Front. Neurosci. 9:377. doi: 10.3389/fnins.2015.00377

INTRODUCTION

According to a developmental perspective, brain homologies across vertebrates are supported by anatomical topographic correspondence and embryonic expression of homeobox and homeobox-like genes. However, species-specific pallial morphology and global gene expression patterns exhibit important dissimilarities at adult stages that would be explained by changes in the differential modulation of pallial developmental programs. In this article we elaborate further the hypothesis that the evolution of the mammalian isocortex required the modulation of conserved developmental patterning programs, providing a new phenotype to the dorsal proliferative compartments. Specifically, this was achieved by virtue of a strong upregulation of dorsal patterning centers like the hem, in combination with the expansion of Pax6 expression that generated a subventricular zone (SVZ) that amplified the proliferation of neuronal progenitors. A third regulating component is provided by the rostral patterning center (RPC), that secretes molecules of the FGF family. Thus, the orchestration and partial overlap of dorsal, lateral and anterior patterning centers gave rise to the laminated mammalian isocortex as an expansion of the dorsal pallial field. This process will be compared to the mechanisms of brain amplification in reptiles and birds, with whom there are both similarities (upregulation of Pax6 signals) and divergences (the dorsal and anterior patterning centers display little upregulation in reptiles and birds).

THE BRAINS OF AMNIOTES

In order to provide the required background to understand the arguments that follow, we will briefly summarize some of the main differences in anatomical brain organization between different amniotes (reptiles, birds and mammals) (Aboitiz et al., 2002, 2003b; Aboitiz and Montiel, 2007b). First, although there are major differences in adult anatomical brain structure, in both mammals and sauropsids (i.e., reptiles and birds) the cerebral hemispheres or telencephali retain the major subdivisions that characterize all vertebrates, i.e., a dorsal component or pallium, receiving most sensory afferents via specialized thalamic nuclei (with the exception of olfaction, that reaches the olfactory cortex directly through the olfactory tract), and a ventral component or subpallium, including the basal ganglia which are involved mainly (but not exclusively) in motor functions. While the subpallium has remained somewhat more conservative in vertebrate evolution, dramatic changes in pallial structure have been observed in the different vertebrate groups, including amniotes.

Pallial Subdivisions

In mammals, the pallium has a relatively simple structure, with a laminar organization that spans the medial pallium (the hippocampus), the dosal pallium (the isocortex) and the lateral pallium (the olfactory cortex), but this laminar pattern is distorted as an aggregate of neurons in the ventral pallial components that contribute to the amygdalar complex. The isocortex is clearly distinguished from the lateral (olfactory cortex) and medial (hippocampal region) pallial derivatives by its conspicuous six-layered structure (as opposed to the three-layered organization of the latter), which in addition is organized into radial columns that derive embryologically from cells following the same radial glial trajectory and in majority are clonally-related (Rakic, 2009; Gao et al., 2014; Vasistha et al., 2014).

In reptiles, the dorsalmost and medial aspects of the pallium are very small and barely make up a primitive layered structure that nonetheless differs from that of the more basal amphibians (the sister group of amniotes) by the existence, in the former, of a limited radial migratory capacity during development, which generates a rudimentary cortex in the adult. On the other hand, in the lateral and ventral pallium, i.e., on the equatorial aspect of the hemisphere, adjacent to the more ventral subpallium, a relatively large structure bulges inside the ventricular cavity, which is termed the dorsal ventricular ridge (DVR). Here we will refer to the anterior component of the DVR, which receives most sensory inputs while its posterior component is agreed to correspond to some amygdalar and subpallial elements (Abellán et al., 2009). As said, the DVR capitalizes most sensory afferences coming from the midbrain to the thalamus (mainly auditory and visual; called collothalamic pathways), while some other sensory afferences that reach directly the thalamus, bypassing the mesencephalon, project to the dorsal and dorsomedial pallium (visual and somatosensory, termed lemnothalamic pathways) (Butler, 1995). In the reptilian lateral pallium, there is also a lateral or olfactory cortex.

In birds, the ancestral DVR has become severely hypertrophied, subdividing into (i) a nidopallium (originating from the ventral pallium and receiving visual and auditory mesencephalic sensory input) and (ii) a mesopallium (originating from the lateral pallium; Medina and Abellán, 2009). Other avian components have also increased in complexity, particularly (iii) the hyperpallium (derived from the dorsal pallium and receiving lemnothalamic visual and somatosensory input), and (iv) the arcopallium (posterior DVR of reptiles, derived from the ventral pallium and subpallium, and comparable to some parts of the mammalian amygdala). All these structures have a morphology that is radically different from that of the isocortex of mammals, as they show no evident signs of laminar or radial organization (although there are important similarities in sensory connectivity and internal circuitry (Jarvis et al., 2005, 2013; Wang et al., 2010; Karten, 2013; Ahumada-Galleguillos et al., 2015; Calabrese and Woolley, 2015). The medial pallium of reptiles and birds is somewhat more conservative, retaining a laminar structure, and is widely considered to be directly comparable to at least parts of the mammalian hippocampus (Striedter, 2015).

Controversies about Homology

Thus, at first sight the brains of sauropsids and mammals are radically different in their anatomical organization. Attempts to establish homologies between these structures have been plagued with controversy, starting with Holmgren's (Holmgren, 1922) early suggestion that the sauropsidian DVR corresponded to components of the amygdalar complex in mammals and the proposal by Ariëns Kappers et al. (1936) that the DVR was a component of the subpallial basal ganglia. The now classical works by Harvey Karten, and by André Parent in the 1960s, established that the DVR was in fact a pallial component, by virtue of its collothalamic sensory afferents (Karten, 1969) and the absence of AChE immunoreactivity, a well-recognized marker of the basal ganglia (Parent and Olivier, 1970). Karten analyzed the collothalamic auditory and visual afferents to the avian nidopallium, noticing a striking similarity between these and the auditory and the so-called extrastriate visual afferents to the mammalian isocortex (both of which are also collothalamic). On the other hand, the portion of the neocortex receiving lemnothalamic visual (striate visual cortex) and somatosensory afferents has sensory connections similar to those in the hyperpallium, a dorsal pallial derivative (Puelles et al., 2000; Aboitiz et al., 2003b; Nomura et al., 2013). Furthermore, recent evidence has appeared showing a similar microcircuitry and input-output organization in the avian nidopallium and the mammalian isocortex (Wang et al., 2010; Ahumada-Galleguillos et al., 2015; Calabrese and Woolley, 2015). Based on this notable evidence, Karten and his associates have strongly advocated for the hypothesis of homology between the circuits in the avian DVR and those in the collothalamic-receiving isocortex (auditory and secondary visual areas). On the other hand, lemnothalamic-receiving isocortical regions (somatosensory and primary visual areas) would correspond to the dorsal cortex or hyperpallium of birds and reptiles, respectively (Butler et al., 2011).

On the other hand, another line of interpretation followed more closely Holmgren's hypothesis of homology between

the DVR and parts of the amygdalar complex of mammals (Aboitiz, 1992; Bruce and Neary, 1995; Striedter, 1997; Puelles et al., 2000; Aboitiz et al., 2003b; Montiel and Molnár, 2013). This line emphasized the expansion of the dorsal pallium (the reptilian dorsal cortex) as the main event in neocortical origins, and assumed that most of the neocortex, including that receiving collothalamic afferents, was of dorsal pallial origin. This perspective received strong support from developmental tracing studies using neural and genetic markers that firmly established a ventral and lateral pallial origin for the sauropsidian DVR (recall, we are referring here to the anterior DVR), as opposed to the isocortex that derives from the dorsal pallium. Nonetheless, this perspective has left open to interpretation the dramatic similarity in sensory and internal connectivity between the avian DVR and the mammalian isocortex. One possibility is that in mammals, the collothalamic afferents were re-routed from the ventral pallium to the dorsal pallium, or that the embryonic territory originally destined to the DVR (lateral or ventral pallium) became phenotypically transformed into dorsal pallium, however maintaining its collothalamic sensory inputs (see below; Aboitiz et al., 2002, 2003b). Another interpretation is that the collothalamic projections to the DVR and the isocortex are not really homologous, there being a collothalamic projection to the mammalian amygdala which would be the most likely homolog of the input to the sauropsidian DVR (Puelles, 2001).

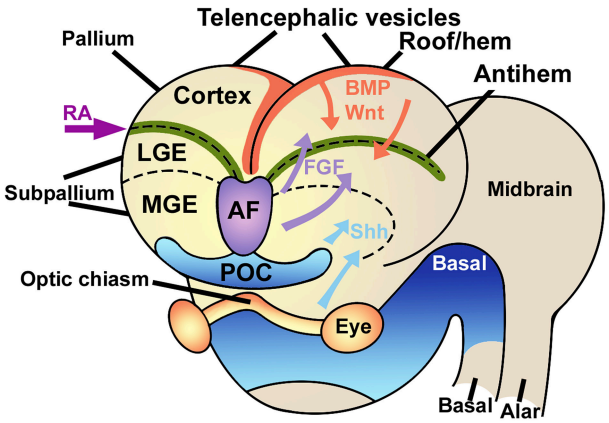


FIGURE 1 | Signaling centers in the embryonic brain. The telencephalic vesicles or cerebral hemispheres are patterned by the combined action of different signaling centers like the rostral-patterning center in the anterior forebrain (AF, violet) secreting FGFs, the dorsal hem (red), secreting Wnts and BMPs, and the antihem (green), which specifies the ventral pallium. Other signaling elements are retinoic acid (RA) laterally and sonic hedgehog (Shh) ventrally. LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; POC, commissural preoptic area. Modified from Medina and Abellán (2009), Sur and Rubenstein (2005) and Aboitiz and Montiel (2012) with permission.

PATTERNING CENTERS IN PALLIAL DEVELOPMENT AND EVOLUTION

We recently developed an hypothesis that attempts to find a common ground for these dissenting interpretations, which prescribes the parallel amplification of a common, ancestral developmental program in the pallium of mammals and sauropsids, yielding brain expansion in both groups but differing in the embryological locus for the expansion (predominantly dorsal pallium in mammals; predominantly lateral/ventral pallium in sauropsids; Aboitiz, 2011). In order to make this hypothesis clearer, we will first discuss some evidence on the embryological development of the mammalian pallium, which is the taxon that has better been studied, particularly the mouse. Evidence to date suggests that these patterning processes are conservative across vertebrates, while we propose that subtle modulations in the absolute and relative activities of these different centers may yield dramatic changes in brain morphology while maintaining a conserved topographic organization.

Patterning Centers of the Mammalian Brain

The embryonic pallium is patterned into distinct embryonic regions by at least three signaling centers, the cortical hem in the mediodorsal region, the antihem in the lateral aspect, and the anterior forebrain in the anteromedial region (**Figure 1**). All these centers secrete specific patterning molecules that diffuse in complementary gradients, generating a regional differentiation matrix that can be experimentally modulated by upregulation or downregulation of each of these signaling centers, yielding expansions of some pallial regions at the expense of others, or transforming the phenotypic identity of some areas (Shimogori et al., 2004).

Specifically, the cortical hem secretes morphogens like BMPs and Wnts, that determine the development of the medial pallium (hippocampus) and establish a posteromedial/high to anterolateral/low gradient along the dorsal pallium, regulating proliferation and patterning of these two structures (Shimogori et al., 2004; O'Leary et al., 2007; Harrison-Uy and Pleasure, 2012). Dorsally derived Wnt factors induce progenitor proliferation at early stages, but are later replaced by the ventrally derived morphogen Pax6 to maintain progenitor cell division (Zhou et al., 2006; Machon et al., 2007; Kuwahara et al., 2010; Harrison-Uy and Pleasure, 2012; **Figure 2**).

Caronia-Brown et al. (2014) recently reported that the cortical hem is a key regulator of both the size and patterning of the neocortex beside the hippocampus, where mice with cortical hem ablations displayed a reduced caudal and dorsomedial neocortex, while the rostral and ventrolateral neocortices expanded normally or increased in relative size. Wnt3a signal from the cortical hem induces self-renewal of radial glia and the early differentiation of cortical intermediate progenitors via the canonical Wnt pathway (Munji et al., 2011). Both opposing roles are modulated by Hipk1 in a dose-dependent mechanism (Marinaro et al., 2012). In the mouse, upregulation of Wnt3a activates the production of intermediate progenitors from radial glial cells increasing the Tbr2-positive cell populations (Kuwahara et al., 2010; Munji et al., 2011; **Figure 2A**). In the Tbr2 KO mouse, the interruption of this cascade leads to a reduction of the intermediate progenitors and a cortical size reduction (Arnold et al., 2008). It has also been found that the transcription factor Lhx2 constraints the development of both the cortical hem and Cajal-Retzius cells, at the expense of favoring

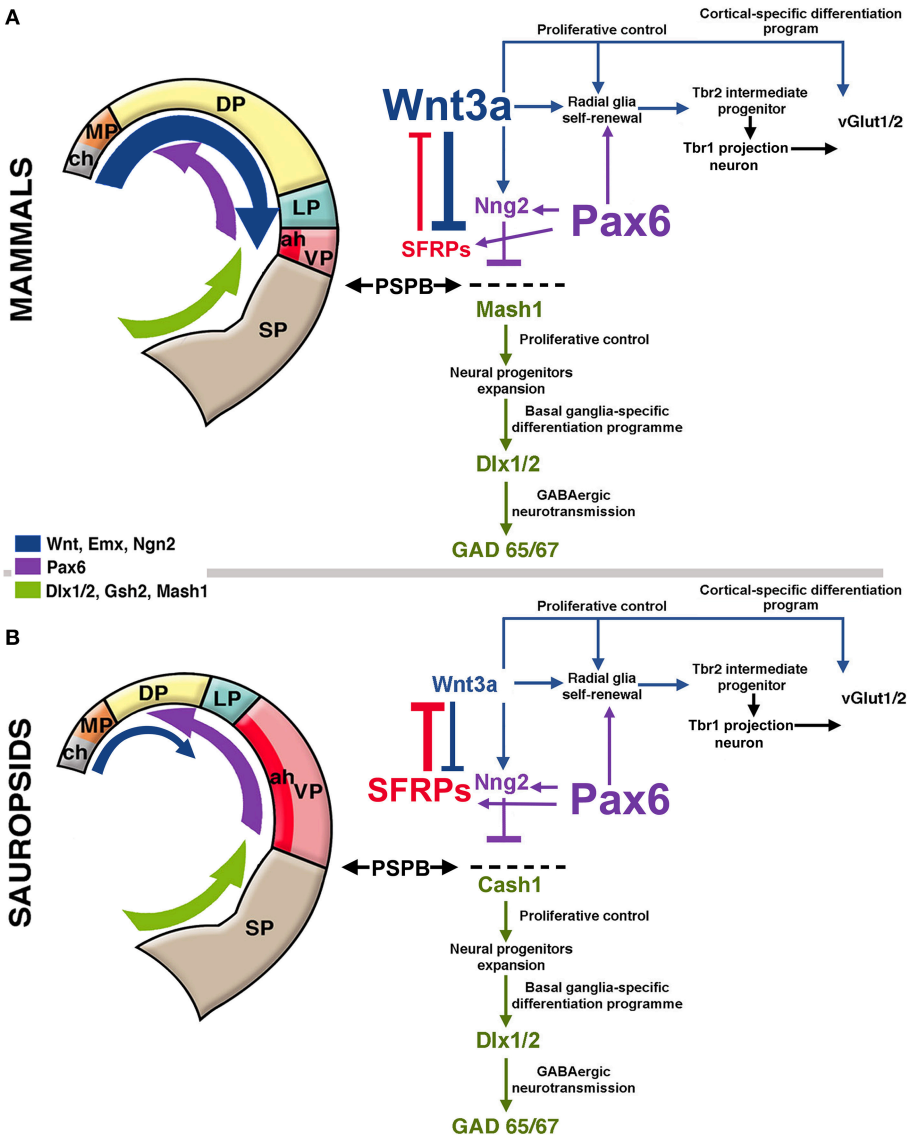


FIGURE 2 | Hypothetical model of telencephalic signaling to drive pallial expansion in mammals and sauropsids. (A) In mammals, dorsal signaling upregulation (blue arrow in the figure) expands the dorsal pallium (DP). In early stages, the upregulation of Wnt3a from the cortical hem (ch, gray in figure) activates the self-renewal of radial glia. In addition, upregulation of ventral factors like Pax6 (purple arrow in the figure) induce late proliferation of radial glia that generate Tbr2+ intermediate progenitors in the SVZ (see diagram at the right). Pax6 also contributes to the formation of the antihem (ah, dark red) that expresses secreted Frizzled-Related Proteins (Sfrp1 and 2; in red) that neutralize the action of dorsally-derived signals like Wnts. Pax6 also activates the expression of the proneural factor neurogenin 1/2 (Sansom et al., 2009) with the consequent inhibition of Mash1 (Cash1 in chicken), a proneural factor highly expressed in subpallial domains. Mash1 induces a cascade that leads to subpallial neural phenotypes (Castro et al., 2011). The pallial/subpallial boundary (PSPB) is defined by the limit of expression of Ngn2 and Mash1 genes (black arrows). **(B)** In sauropsids, the dorsalizing activity of the cortical hem remains reduced, but like in mammals, there is an upregulation of Pax6, leading to the expansion of the antihem as there is little dorsal activity to counteract it. While in mammals there is a strong superposition of lateral/ventral signals and dorsal signals, in sauropsids lateral/ventral signals tend to be more decisive for pallial patterning.

the development of the cortical neuroepithelium including the hippocampus (Bulchand et al., 2001; Roy et al., 2014).

Of note, the corpus callosum, the largest tract in the brain and a unique character of placental mammals, originates dorsally to the hippocampal commissure common to all vertebrates (Aboitiz and Montiel, 2003; Aboitiz et al., 2003a). Marsupials and monotremes also have interhemispheric connections (which are actually unique to mammals), but these cross through the anterior commissure located in the anterior forebrain. Recently, the cellular and molecular mechanisms involved in the generation of the corpus callosum have been analyzed by the group of Linda Richards, implying a critical role of the commissural plate, particularly the cortical hem, in establishing the anatomical and molecular substrate for the development of interhemispheric connections along the nascent corpus callosum (Suárez et al., 2014).

More laterally in the pallium, the antihem expresses different EGFs, FGFs and especially Frizzled-related proteins that antagonize the effects of dorsal morphogens secreted by the cortical hem, and are considered to specify the ventral pallial territory (Assimacopoulos et al., 2003; **Figure 2**). Noticeably, Pax6 signaling induces the antihem, and is strongly expressed in the ventral pallium and equatorial aspect of the hemisphere, showing a gradient of activity from the anterolateral to the caudomedial hemisphere. Pax6 is required for the development of lateral and ventral pallial identities (olfactory and amygdalar components; Piñon et al., 2008; Cocas et al., 2011), and patterns the anterolateral neocortex (Bishop et al., 2000). Pax6 is a critical promotor of progenitor proliferation, and an essential component for the evolutionary expansion of the neocortex (Poluch and Juliano, 2015). The developmental expression pattern of signaling factors is mostly conserved between chick and mouse, but a broader expression of Pax6 is detected in the ventral pallium of chick (Frowein et al., 2002; Assimacopoulos et al., 2003). For this reason, we proposed this to be a prime candidate for a proliferative signal in all amniotes (Aboitiz, 2011; Aboitiz and Zamorano, 2013), triggering a conserved differentiation cascade in both sauropsids and mammals. Additional candidates to stimulate progenitor amplification are regulators of Notch, which controls the stem cell cycle and neurogenesis and is highly expressed in reptiles like the gecko (Nomura et al., 2013, 2014), POU homeobox factors (Dominguez et al., 2013) and other proteins that regulate progenitor proliferation (Vied et al., 2014).

The third patterning center, located in the anterior forebrain is the rostral patterning center (RPC), which secretes molecules of the FGF family and promotes ventral and anterior telencephalic fates (Rubenstein, 2011). FGF signaling from the RPC has a strong role in patterning not only the neocortex but also the diencephalon and ventral telencephalon, In addition, FGF signaling is required for the generation of commissural connectivity as well as differentiation of the dorsal midline (Shanmugalingam et al., 2000).

From a comparative perspective, the RPC may be closely related to the anterior neural ridge, located in the frontal edge of the head, in front of the most anterior neural tissue, which is also characterized by strong expression of FGF8 and other members of the FGF family (Pownall and Isaacs, 2010). The anterior neural ridge induces the olfactory and adenohypophyseal placodes, both of which apparently derive from a primitive panplacodal primordium (Schlosser, 2005). The role of FGF signaling in telencephalic patterning has been observed even in basal vertebrates like the lamprey (Sugahara et al., 2011), which indicates its conservatism in evolution, possibly in association with the evolution of olfaction (Aboitiz and Montiel, 2007a,b).

The RPC expresses a variety of FGF factors, of which FGF8 has been the most studied in relation to forebrain and cortical patterning. During embryogenesis, FGF8 diffuses caudally from the anterior forebrain, promoting ventral and anterior phenotypes and inducing progenitor proliferation (Borello et al., 2008; Toyoda et al., 2010). FGF8 induces the expression of FOXG1, which antagonizes the activity of the dorsal morphogen BMP (Shimamura and Rubenstein, 1997). Furthermore, FGF8 is strongly required for frontal cortex differentiation, and while hypomorphic expression in mutant mice leads to reductions in frontal cortex size and expansion of caudal markers, its ectopic overexpression has resulted in the generation of an additional somatosensory cortex and thalamus (Fukuchi-Shimogori and Grove, 2001). Noteworthy, FGF8 can regulate postnatal thalamic innervation and the intracortical wiring pattern, even if the initial connectivity pattern is not affected in newborn FGF8 mutants (see Danjo et al., 2011). Other members of the FGF family have been found to have similar effects in brain development. For example, like FGF8, mutations in FGF17 produce frontal, midbrain and cerebellar alterations, as well as behavioral deficits reminiscent of autistic spectrum symptomatology. Furthermore, progenitors generated in the RPC contribute neurons to wide regions of the telencephalon, including medial prefrontal cortex (Hoch et al., 2015). There is evidence that FGF2-sensitive neural stem cells (expressing Fgfr1) are required for hippocampal growth (Ohkubo et al., 2004), but it is not clear that FGF2 derives from the RPC (Rubenstein, 2011).

Finally, the cortical hem, the antihem and the anterior forebrain (but particularly the cortical hem), are the sites of generation of Cajal-Retzius cells that secrete the glycoprotein reelin, required for proper neocortical lamination and dendritic growth of pyramidal neurons (Nomura et al., 2008; Meyer, 2010; Kupferman et al., 2014; Martínez-Cerdeño and Noctor, 2014).

A UNIFYING HYPOTHESIS

Considering the above evidence, we have outlined an hypothesis that considers both the developmental and the phenotypic comparative evidence, thus attempting to account for both perspectives of pallial homology in amniotes (Aboitiz, 2011; Aboitiz and Montiel, 2012; Aboitiz and Zamorano, 2013). This hypothesis is based on the differential modulation of telencephalic patterning centers in sauropsids and mammals, and, as we suggest in this article, on the overlap of distinct morphogenetic fields only in mammals, which yielded the expansion of the isocortex in this group.

Shared, Pax6- Dependent Brain Amplification

We have proposed that the expansion of both the avian pallium and the mammalian isocortex relied on cascades driven by several, phylogenetically conserved neurogenetic factors. One likely candidate is Pax6, which promotes progenitor division and the extension of neurogenesis. Pax6 is maximally expressed in lateral and ventral pallial regions, decreasing its expression in the rostrocaudal direction. In addition to this spatial gradient, there is also a temporal gradient of Pax6 expression from the anteroventral to the rostrocaudal pallium (Aboitiz et al., 2003b; Aboitiz and Montiel, 2007b, 2012; Aboitiz and Zamorano, 2013). The conservation of this signaling cascade may explain the phenotypic concordance of lateral and ventral pallial cells in the sauropsidian brain and cells in the upper isocortical layers (derived from the dorsal pallium). The latter are considered to be, in general, phylogenetically newer than lower isocortical layers

as they derive from the embryonic subventricular zone (SVZ), a compartment for late progenitor proliferation that is found in the embryonic precursors of both the avian DVR and the mammalian isocortex (Reiner, 1991; Cheung et al., 2007; for reviews see Aboitiz et al., 2001, 2003b). The SVZ develops due to an amplification of Pax6 signaling in the radial glia of the VZ, whose progeny migrates to the SVZ and expresses the marker Tbr2 (see Englund et al., 2005; Ypsilanti and Rubenstein, 2015). Recently, Martínez-Cerdeño et al. (2015) have shown that in the turtle and avian DVR (lateral/ventral pallium), and in the mammalian isocortex, Pax6-expressing radial glia give rise to Tbr2-expressing intermediate progenitors that migrate into the SVZ. Most notably, in the DVR of the lizard and in the dorsal cortex of turtle and lizard, no distinct SVZ could be seen, while scattered Tbr2+ cells could be found in the VZ (Montiel et al., 2015). This resembles early developmental stages in mammals, where Tbr2+ cells can be found in the VZ before the SVZ becomes a distinct layer (Noctor et al., 2008). This evidence is consistent with our previous hypothesis of a conserved program of brain expansion in amniotes (Aboitiz, 2011; Aboitiz and Montiel, 2012; Aboitiz and Zamorano, 2013).

Overlap between Dorsal and Ventral Morphogenetic Fields in Mammals

Thus, there is evidence supporting a conserved developmental schedule in the pallium of amniotes (and possibly in other vertebrates). But this leaves open a fundamental question that has not yet been properly addressed: why in mammals a laminated structure became established, while in sauropsids the non-laminar condition prevails? In our view, this results from the additional amplification of the dorsal and anterior signaling centers (the cortical hem and RPC), that together with the proliferation of Cajal-Retzius cells, promoted a pyramidal morphology in excitatory cells, and a columnar organization to the isocortex. Thus, in addition to the latero-ventral pallial driven amplification of progenitor proliferation, the mammalian brain would have suffered a process of "dorsalization" in its development, where dorsal signaling factors became upregulated and determined a conspicuous laminar organization in the dorsal pallium, aided by the amplification of reelin-producing Cajal-Retzius cells (Aboitiz et al., 2003b). In this account, it is conceivable that the boundaries between the dorsal and the lateral/ventral pallium became shifted so that territory originally destined to the future DVR became partially transformed into a cortical phenotype, while maintaining its original collothalamic afferences. As said, another option is that collothalamic afferents were re-routed into the expanding dorsal pallium (Aboitiz et al., 2002, 2003b). Overall, this hypothesis has the virtue of reconciling the developmental and the phenotypic evidences into one overarching developmental-evolutionary process.

Overall, the point is that a similar developmental cascade to enhance progenitor proliferation and increasing neuronal numbers (presumably depending on Pax6 and associated with the development of a SVZ) became activated in both birds and mammals. This process took place in the lateral and ventral pallium of birds, and in the dorsal pallium of mammals, in the latter contributing to the generation of late-produced superficial isocortical layers. Our hypothesis implies that although Pax6 has been upregulated in both lineages, only in mammals there is a concomitant upregulation of the cortical hem that limits the expansion of the antihem but has no strong effect in Pax6 activity (Aboitiz, 2011; Aboitiz and Montiel, 2012; Aboitiz and Zamorano, 2013). In fact, there is a superposition of dorsal, hem-related signals like Emx2 and Pax6 in the developing neocortex, which contribute to aeral patterning of this structure (O'Leary and Sahara, 2008).

Temporal Segregation between Dorsal and Ventral Patterning Centers

Some authors have advanced the concept of a spatial-to-temporal transformation of the differentiation programs of neuronal types in sauropsids and mammals (Nomura et al., 2009; Suzuki et al., 2012). Thus, neurons in the more conservative mediodorsal pallium of sauropsids tend to express markers that are also found in lower isocortical layers in mammals; while mammalian mid- and upper isocortical markers tend to be found in the most expanding ventral, lateral and dorsal pallial regions (for more details see Table 1 in Aboitiz and Zamorano, 2013); see also (Nomura et al., 2009; Suzuki et al., 2012; Belgard et al., 2013). An additional hypothesis has been put forward by Federico Luzzati (2015), who noticed a similar expression of markers like DCX/Tbr1 in the lateral (olfactory) cortex of reptiles and the superficial layers of the mammalian isocortex. Luzzati proposes that the emerging, dorsal pallial, mammalian isocortex co-opted a lateral pallial developmental program to generate the superficial isocortical layers, a possibility that is in general terms consistent with ours.

Thus, deep isocortical layers show a different phenotype than the superficial ones, which share more markers with the lateral pallial neurons of sauropsids. In this line, there may be a differential timing in the activity of hem-derived transcription factors and of Pax6, especially considering that the cortical hem has been found to be a strong regulator of the size of the neocortex (Caronia-Brown et al., 2014) and that Wnts induce progenitor proliferation at early stages (Zhou et al., 2006; Machon et al., 2007; Kuwahara et al., 2010; Harrison-Uy and Pleasure, 2012). Early Wnt activity (or other dorsal factors) might contribute to specify the deep layer isocortical neurons, with dorsal pallial phenotypes. On the other hand, there are different Pax6 transcripts expressed in different developmental stages, with partly antagonist activities among them, that may fine-regulate the extent of progenitor proliferation (Ypsilanti and Rubenstein, 2015). Furthermore, a recent article reports the existence of a lineage-restricted population of radial glia that engages in neurogenic divisions only in late development, giving rise to neocortical supragranular neurons and particularly callosal-projecting neurons (García-Moreno and Molnár, 2015). Moreover, this type of late-engaging progenitors was not observed in sauropsids. It may be that early dorsalizing factors are producing a delay in the neurogenic activity of Pax6 activity, which becomes expressed in late development. The progeny of these late, Pax6-driven cells, might share features with early produced neurons in the lateral pallium, as proposed by several authors (Nomura et al., 2009; Suzuki et al., 2012; Luzzati, 2015).

Finally, the hem-derived Cajal-Retzius cells might also contribute to laminar specification in late developmental stages, promoting a columnar organization of the cells of the cortical plate.

Genetic but Not Regional Homology

The main discussion regarding the comparisons of avian and mammalian brains relies on the issue of homology, i.e., to what extent these similarities can be tracked to a common ancestor. In our opinion, homology is not an all-or-none condition but depends on the phenomenical level at which it is observed (De Beer, 1971; Aboitiz, 1988; Striedter and Northcutt, 1991). There may not be regional homology between the isocortex and the DVR as both structures derive from different embryonic regions (dorsal pallium and lateral/ventral pallium, respectively). Nonetheless, some early embryonic territory destined to the lateral-ventral pallium may have acquired a dorsal pallial identity by influence of the expanding cortical hem, which again would cast doubts about the strict meaning of homology (i.e., do the progenitor cell populations or the developmental fields determine homology?).

On the other hand, the genetic cascades involved in brain growth are partly the same, regardless of pallial region (lateroventral pallium in sauropsids, dorsal pallium in mammals); and they presumably depend on Pax6 signaling to amplify the progenitor cell population. In other words, an upregulation of Pax6 or related signals was independently recruited in birds and mammals to amplify progenitor cell population, an instance of co-option of a shared developmental program in a new context (Aboitiz and Montiel, 2007a). Thus, in the common ancestor, the morphogenetic fields specified by Pax6 activity (including the antihem), the cortical hem and the anterior forebrain may have suffered little overlap, generating a spatial, or tangential gradient of neuronal differentiation. This situation was probably maintained in reptiles and to some extent also in birds. Nonetheless, in mammals this becomes complicated by the additional influence of the cortical hem and anterior forebrain. Concurrent amplification of all these signaling centers in early mammals yielded an extensive overlap between their respective morphogenetic fields, and contributed to the establishment of a temporal, or radial gradient of differentiation in the nascent isocortex. Dorsalizing factors acted at early stages, determining the phenotypes of early-produced inferior layer neurons, while Pax6 amplification exerted its effects at later stages, which together with Cajal-Retzius cells determined the phenotypes of late-produced, superficial layer neurons. There is some evidence that is consistent with this view, as the cortical hem is present but is much less developed in the sauropsids that have been studied than in mammals, showing decreased specific markers like cWnt8b and a much smaller population of Cajal-Retzius cells (Cabrera-Socorro et al., 2007; Medina and Abellán, 2009; Subramanian et al., 2009; Abellán et al., 2010). In birds and reptiles, there are scattered cells with a Cajal-Retzius typical morphology, but these are not nearly as abundant as in mammals and express much lower levels of reelin. Finally, this proposal predicts that as the isocortex increases in size by amplification of genes like Pax6 and others, there is a growing influence from the cortical hem to maintain its laminar structure and patterning (Tarabykin et al., 2001; Tuoc et al., 2009; Caronia-Brown et al., 2014).

Hippocampus and Olfactory Cortex

The cortical hem is also critical for the development of the mammalian dentate gyrus and hippocampus, components that have evidenced a significant increase in size and complexity in mammals (Hevner, 2015), although not comparable with the expansion of the isocortex. Thus, there is still the question of why did the former structures, that depend most directly on the cortical hem, did not expand explosively as the isocortex did. It is possible that there are some yet unknown factors, perhaps related to a decreased activity of Pax6 signaling in dorsomedial regions, or to activity from the RPC, that may restrict the expansion of the embryonic medial pallium (hippocampus and dental gyrus), but at the same time be permissive for dorsal pallial expansion (giving rise to the isocortex).

Likewise, early mammals displayed a moderate expansion of the olfactory cortex before the isocortex took off (Rowe and Shepherd, 2015). We suggest that the early expansion of both, the mammalian olfactory cortex and the reptilian DVR, was probably driven by a moderate upregulation of Pax6 activity in both groups. However, in early mammals and reptiles, there may have been different selective pressures on sensory processing: olfaction in mammals and vision in reptiles. Perhaps natural selection favored the activation of distinct Pax6-dependent, tissue-specific enhancers in mammals and reptiles (see Ypsilanti and Rubenstein, 2015), that promoted the development of the olfactory cortex in mammals and the DVR in reptiles, to support vision in the latter. In later stages of mammalian evolution, Wnt activity became upregulated, leading isocortical expansion, and restricting the relative sizes of the olfactory cortex and amygdala, as evidenced by their inverse scaling with isocortical size across mammals (Reep et al., 2007).

Although significant, the expansion of the olfactory cortex in early mammals was limited for at least two reasons: (1) The brain of mammal-like ancestors was already small, and (2) There are functional limits to the radial expansion of the olfactory cortex, which relies strongly in tangential, associative interactions (Rowe and Shepherd, 2015). Although the neocortex inherits the same tangential organization, it superimposes a radial arrangement over it, associated to the development of a SVZ (see Bosman and Aboitiz, 2015).

SUMMARY

In this article, we have reviewed developmental evidence supporting the concept that the origin of the mammalian brain relies on the amplification of several morphogenetic centers that participate in patterning the dorsal cerebral hemisphere or pallium. Furthermore, we claim that there are conserved molecular mechanisms for progenitor cell division and neuronal differentiation at least in all amniotes, which may rely on a cascade associated to Pax6 and other genes, which act in a lateral-to-dorsomedial gradient thereby tending to differentiate and augment ventral and lateral pallial phenotypes. However, mammals underwent a diverging trend by, in addition,

enhancing the activity of dorsomedial and anterior telencephalic signaling centers (the anterior forebrain and the cortical hem, respectively) that, together with the proliferation of reelin-producing Cajal-Retzius cells, induced a laminar arrangement and a characteristic pyramidal cell shape for excitatory neurons in the medial and dorsal pallium (note that a rudimentary laminar arrangement of pyramidal cells already exists in the cortex of reptiles and in the olfactory cortex of mammals). Morphogens derived from these centers also restricted the expansion of the antihem in the lateral and ventral pallium, and favored the generation of a dorsal pallial neocortex that was initially small, with a relatively large olfactory cortex, as in basal therian mammals. Thus, a differentiation gradient that was ancestrally established in the tangential axis, became expressed in the radial domain by virtue of the superposition of the different signaling molecules that acted at different developmental stages, i.e., dorsal-derived Wnts at early stages, and laterally-derived Pax6 signals at late developmental stages. In subsequent lineages, the isocortex expanded enormously both in absolute and relative size. In line with these arguments, Lewitus et al. (2014) have recently proposed that the ancestor of crown mammals might have had a gyrencephalic brain with a well differentiated isocortex, which would imply that the origin of isocortex is to be traced back to earlier mammalian groups, possibly living in the Jurassic period (Luo, 2007; Lee and Beck, 2015).

ACKNOWLEDGMENTS

Funded by the Millennium Center for the Neuroscience of Memory, Chile, Grant No. NC10-001-F to FA. We are also grateful to the reviewers of this article, with forced us to clarify important issues and contributed with innovative ideas during the elaboration of this manuscript.

REFERENCES

Abellán, A., Legaz, I., Vernier, B., Rétaux, S., and Medina, L. (2009). Olfactory and amygdalar structures of the chicken ventral pallium based on the combinatorial expression patterns of LIM and other developmental regulatory genes. *J. Comp. Neurol.* 516, 166–186. doi: 10.1002/cne.22102

Abellán, A., Menuet, A., Dehay, C., Medina, L., and Rétaux, S. (2010). Differential expression of LIM-homeodomain factors in Cajal-Retzius cells of primates, rodents, and birds. *Cereb. Cortex* 20, 1788–1798. doi: 10.1093/cercor/bhp242

Aboitiz, F. (1988). Homology: a comparative or a historical concept? *Acta Biotheor.* 37, 27–29.

Aboitiz, F. (1992). The evolutionary origin of the mammalian cerebral cortex. *Biol. Res.* 25, 41–49.

Aboitiz, F. (2011). Genetic and developmental homology in amniote brains. Toward conciliating radical views of brain evolution. *Brain Res. Bull.* 84, 125–136. doi: 10.1016/j.brainresbull.2010.12.003

Aboitiz, F., López, J., and Montiel, J. (2003a). Long distance communication in the human brain: timing constraints for inter-hemispheric synchrony and the origin of brain lateralization. *Biol. Res.* 36, 89–99. doi: 10.4067/S0716-97602003000100007

Aboitiz, F., and Montiel, J. (2003). One hundred million years of interhemispheric communication: the history of the corpus callosum. *Braz. J. Med. Biol. Res.* 36, 409–420. doi: 10.1590/S0100-879X2003000400002

Aboitiz, F., and Montiel, J. (2007a). Co-option of signaling mechanisms from neural induction to telencephalic patterning. *Rev. Neurosci.* 18, 311–342. doi: 10.1515/REVNEURO.2007.18.3-4.311

Aboitiz, F., and Montiel, J. (2007b). Origin and evolution of the vertebrate telencephalon, with special reference to the mammalian neocortex. *Adv. Anat. Embryol. Cell Biol.* 193, 1–112. doi: 10.1007/978-3-540-49761-5

Aboitiz, F., and Montiel, J. F. (2012). From tetrapods to primates: conserved developmental mechanisms in diverging ecological adaptations. *Prog. Brain Res.* 195, 3–24. doi: 10.1016/B978-0-444-53860-4.00001-5

Aboitiz, F., Montiel, J., Morales, D., and Concha, M. (2002). Evolutionary divergence of the reptilian and the mammalian brains: considerations on connectivity and development. *Brain Res. Brain Res. Rev.* 39, 141–153. doi: 10.1016/S0165-0173(02)00180-7

Aboitiz, F., Morales, D., and Montiel, J. (2001). The inverted neurogenetic gradient of the mammalian isocortex: development and evolution. *Brain Res. Brain Res. Rev.* 38, 129–139. doi: 10.1016/S0006-8993(01)02902-X

Aboitiz, F., Morales, D., and Montiel, J. (2003b). The evolutionary origin of the mammalian isocortex: towards an integrated developmental and functional approach. *Behav. Brain Sci.* 26, 535–552. discussion 552–585. doi: 10.1017/S0140525X0326012X

Aboitiz, F., and Zamorano, F. (2013). Neural progenitors, patterning and ecology in neocortical origins. *Front. Neuroanat.* 7:38. doi: 10.3389/fnana.2013.00038

Ahumada-Galleguillos, P., Fernández, M., Marin, G. J., Letelier, J. C., and Mpodozis, J. (2015). Anatomical organization of the visual dorsal ventricular ridge in the chick (*Gallus gallus*): layers and columns in the avian pallium. *J. Comp. Neurol.* 523, 2618–2636. doi: 10.1002/cne.23808

Ariëns Kappers, C. V., Huber, C. G., and Crosby, E. C. (1936). *The Comparative Anatomy of the Nervous System of Vertebrates, Including Man*. New York, NY: Hafner.

Arnold, S. J., Huang, G. J., Cheung, A. F. P., Era, T., Nishikawa, S. I., Bikoff, E. K., et al. (2008). The T-box transcription factor Eomes/Tbr2 regulates neurogenesis in the cortical subventricular zone. *Genes Dev.* 22, 2479–2484. doi: 10.1101/gad.475408

Assimacopoulos, S., Grove, E. A., and Ragsdale, C. W. (2003). Identification of a Pax6-dependent epidermal growth factor family signaling source at the lateral edge of the embryonic cerebral cortex. *J. Neurosci.* 23, 6399–6403. doi: 10.1002/cne.903070312

Belgard, T. G., Montiel, J. F., Wang, W. Z., García-Moreno, F., Margulies, E. H., Ponting, C. P., et al. (2013). Adult pallium transcriptomes surprise in not reflecting predicted homologies across diverse chicken and mouse pallial sectors. *Proc. Natl. Acad. Sci. U.S.A.* 110, 13150–13155. doi: 10.1073/pnas.1307444110

Bishop, K. M., Goudreau, G., and O'Leary, D. D. (2000). Regulation of area identity in the mammalian neocortex by Emx2 and Pax6. *Science* 288, 344–349. doi: 10.1126/science.288.5464.344

Borello, U., Cobos, I., Long, J. E., McWhirter, J. R., Murre, C., and Rubenstein, J. L. R. (2008). FGF15 promotes neurogenesis and opposes FGF8 function during neocortical development. *Neural Dev.* 3:17. doi: 10.1186/1749-8104-3-17

Bosman, C. A., and Aboitiz, F. (2015). Functional constraints in the evolution of brain circuits. *Front. Neurosci.* 9:303. doi: 10.3389/fnins.2015.00303

Bruce, L. L., and Neary, T. J. (1995). The limbic system of tetrapods: a comparative analysis of cortical and amygdalar populations. *Brain Behav. Evol.* 46, 224–234. doi: 10.1159/000113276

Bulchand, S., Grove, E. A., Porter, F. D., and Tole, S. (2001). LIM-homeodomain gene Lhx2 regulates the formation of the cortical hem. *Mech. Dev.* 100, 165–175. doi: 10.1016/S0925-4773(00)00515-3

Butler, A. B. (1995). The dorsal thalamus of jawed vertebrates - a comparative viewpoint. *Brain Behav. Evol.* 46, 209–223. doi: 10.1159/000113275

Butler, A. B., Reiner, A., and Karten, H. J. (2011). Evolution of the amniote pallium and the origins of mammalian neocortex. *Ann. N. Y. Acad. Sci.* 1225, 14–27. doi: 10.1111/j.1749-6632.2011.06006.x

Cabrera-Socorro, A., Hernandez-Acosta, N. C., Gonzalez-Gomez, M., and Meyer, G. (2007). Comparative aspects of p73 and Reelin expression in Cajal-Retzius

cells and the cortical hem in lizard, mouse and human. *Brain Res.* 1132, 59–70. doi: 10.1016/j.brainres.2006.11.015

Calabrese, A., and Woolley, S. M. N. (2015). Coding principles of the canonical cortical microcircuit in the avian brain. *Proc. Natl. Acad. Sci. U.S.A.* 112, 3517–3522. doi: 10.1073/pnas.1408545112

Caronia-Brown, G., Yoshida, M., Gulden, F., Assimacopoulos, S., and Grove, E. A. (2014). The cortical hem regulates the size and patterning of neocortex. *Development* 141, 2855–2865. doi: 10.1242/dev.106914

Castro, D. S., Martynoga, B., Parras, C., Ramesh, V., Pacary, E., Johnston, C., et al. (2011). A novel function of the proneural factor Ascl1 in progenitor proliferation identified by genome-wide characterization of its targets. *Genes Dev.* 25, 930–945. doi: 10.1101/gad.627811

Cheung, A. F. P., Pollen, A. A., Tavare, A., DeProto, J., and Molnár, Z. (2007). Comparative aspects of cortical neurogenesis in vertebrates. *J. Anat.* 211, 164–176. doi: 10.1111/j.1469-7580.2007.00769.x

Cocas, L. A., Georgala, P. A., Mangin, J.-M., Clegg, J. M., Kessaris, N., Haydar, T. F., et al. (2011). Pax6 is required at the telencephalic pallial-subpallial boundary for the generation of neuronal diversity in the postnatal limbic system. *J. Neurosci.* 31, 5313–5324. doi: 10.1523/JNEUROSCI.3867-10.2011

Danjo, T., Eiraku, M., Muguruma, K., Watanabe, K., Kawada, M., Yanagawa, Y., et al. (2011). Subregional specification of embryonic stem cell-derived ventral telencephalic tissues by timed and combinatory treatment with extrinsic signals. *J. Neurosci.* 31, 1919–1933. doi: 10.1523/JNEUROSCI.5128-10.2011

De Beer, G. (1971). *Homology, an Unsolved Problem*. Glasgow: Oxford University Press.

Dominguez, M. H., Ayoub, A. E., and Rakic, P. (2013). POU-III transcription factors (Brn1, Brn2, and Oct6) influence neurogenesis, molecular identity, and migratory destination of upper-layer cells of the cerebral cortex. *Cereb. Cortex* 23, 2632–2643. doi: 10.1093/cercor/bhs252

Englund, C., Fink, A., Lau, C., Pham, D., Daza, R. A., Bulfone, A., et al. (2005). Pax6, Tbr2, and Tbr1 are expressed sequentially by radial glia, intermediate progenitor cells, and postmitotic neurons in developing neocortex. *J. Neurosci.* 25, 247–251. doi: 10.1523/JNEUROSCI.2899-04.2005

Frowein, J., Campbell, K., and Götz, M. (2002). Expression of Ngn1, Ngn2, Cash1, Gsh2 and Sfrp1 in the developing chick telencephalon. *Mech. Dev.* 110, 249–252. doi: 10.1016/S0925-4773(01)00590-1

Fukuchi-Shimogori, T., and Grove, E. A. (2001). Neocortex patterning by the secreted signaling molecule FGF8. *Science* 294, 1071–1074. doi: 10.1126/science.1064252

Gao, P., Postiglione, M. P., Krieger, T. G., Hernandez, L., Wang, C., Han, Z., et al. (2014). Deterministic progenitor behavior and unitary production of neurons in the neocortex. *Cell* 159, 775–788. doi: 10.1016/j.cell.2014.10.027

García-Moreno, F., and Molnár, Z. (2015). Subset of early radial glial progenitors that contribute to the development of callosal neurons is absent from avian brain. *Proc. Natl. Acad. Sci. U.S.A.* 112, E5058–E5067. doi: 10.1073/pnas.1506377112

Harrison-Uy, S. J., and Pleasure, S. J. (2012). Wnt signaling and forebrain development. *Cold Spring Harb. Perspect. Biol.* 4:a008094. doi: 10.1101/cshperspect.a008094

Hevner, R. F. (2015). Evolution of the mammalian dentate gyrus. *J. Comp. Neurol.* doi: 10.1002/cne.23851. [Epub ahead of print].

Hoch, R. V., Clarke, J. A., and Rubenstein, J. L. (2015). Fgf signaling controls the telencephalic distribution of Fgf-expressing progenitors generated in the rostral patterning center. *Neural Dev.* 10, 8. doi: 10.1186/s13064-015-0037-7

Holmgren, N. (1922). Points of view concerning forebrain morphology in lower vertebrates. *J. Comp. Neurol.* 34, 391–459. doi: 10.1002/cne.900340502

Jarvis, E. D., Güntürkün, O., Bruce, L., Csillag, A., Karten, H., Kuenzel, W., et al. (2005). Avian brains and a new understanding of vertebrate brain evolution. *Nat. Rev. Neurosci.* 6, 151–159. doi: 10.1038/nrn1606

Jarvis, E. D., Yu, J., Rivas, M. V., Horita, H., Feenders, G., Whitney, O., et al. (2013). Global view of the functional molecular organization of the avian cerebrum: mirror images and functional columns. *J. Comp. Neurol.* 521, 3614–3665. doi: 10.1002/cne.23404

Karten, H. J. (1969). The organization of the avian telencephalon and some speculations on the phylogeny of the amniote telencephalon. *Ann. N.Y. Acad. Sci.* 167, 164–179. doi: 10.1111/j.1749-6632.1969.tb20442.x

Karten, H. J. (2013). Neocortical evolution: neuronal circuits arise independently of lamination. *Curr. Biol.* 23, R12–R15. doi: 10.1016/j.cub.2012.11.013

Kupferman, J. V., Basu, J., Russo, M. J., Guevarra, J., Cheung, S. K., and Siegelbaum, S. A. (2014). Reelin signaling specifies the molecular identity of the pyramidal neuron distal dendritic compartment. *Cell* 158, 1335–1347. doi: 10.1016/j.cell.2014.07.035

Kuwahara, A., Hirabayashi, Y., Knoepfler, P. S., Taketo, M. M., Sakai, J., Kodama, T., et al. (2010). Wnt signaling and its downstream target N-myc regulate basal progenitors in the developing neocortex. *Development* 137, 1035–1044. doi: 10.1242/dev.046417

Lee, M. S. Y., and Beck, R. M. D. (2015). Mammalian evolution: a Jurassic spark. *Curr. Biol.* 25, pR759–pR761. doi: 10.1016/j.cub.2015.07.008

Lewitus, E., Kelava, I., Kalinka, A. T., Tomancak, P., and Huttner, W. B. (2014). An adaptive threshold in mammalian neocortical evolution. *PLoS Biol.* 12:e1002000. doi: 10.1371/journal.pbio.1002000

Luo, Z.-X. (2007). Transformation and diversification in early mammal evolution. *Nature* 450, 1011–1019. doi: 10.1038/nature06277

Luzzati, F. (2015). A hypothesis for the evolution of the upper layers of the neocortex through co-option of the olfactory cortex developmental program. *Front. Neurosci.* 9:162. doi: 10.3389/fnins.2015.00162

Machon, O., Backman, M., Machonova, O., Kozmik, Z., Vacik, T., Andersen, L., et al. (2007). A dynamic gradient of Wnt signaling controls initiation of neurogenesis in the mammalian cortex and cellular specification in the hippocampus. *Dev. Biol.* 311, 223–237. doi: 10.1016/j.ydbio.2007.08.038

Marinaro, C., Pannese, M., Weinandy, F., Sessa, A., Bergamaschi, A., Taketo, M. M., et al. (2012). Wnt signaling has opposing roles in the developing and the adult brain that are modulated by Hipk1. *Cereb. Cortex* 22, 2415–2427. doi: 10.1093/cercor/bhr320

Martínez-Cerdeño, V., Cunningham, C. L., Camacho, J., Keiter, J. A., Ariza, J., Lovern, M., et al. (2015). Evolutionary origin of Tbr2-expressing precursor cells and the subventricular zone in the developing cortex. *J. Comp. Neurol.* doi: 10.1002/cne.23879. [Epub ahead of print].

Martínez-Cerdeño, V., and Noctor, S. C. (2014). Cajal, Retzius, and Cajal-Retzius cells. *Front. Neuroanat.* 8:48. doi: 10.3389/fnana.2014.00048

Medina, L., and Abellán, A. (2009). Development and evolution of the pallium. *Semin. Cell Dev. Biol.* 20, 698–711. doi: 10.1016/j.semcdb.2009.04.008

Meyer, G. (2010). Building a human cortex: the evolutionary differentiation of Cajal-Retzius cells and the cortical hem. *J. Anat.* 217, 334–343. doi: 10.1111/j.1469-7580.2010.01266.x

Montiel, J. F., and Molnár, Z. (2013). The impact of gene expression analysis on evolving views on avian brain organization. *J. Comp. Neurol.* 521, 3604–3613. doi: 10.1002/cne.23403

Montiel, J. F., Vasistha, N. A., Garcia-Moreno, F., and Molnár, Z. (2015). From sauropsids to mammals and back: new approaches to comparative cortical development. *J. Comp. Neurol.* doi: 10.1002/cne.23871. [Epub ahead of print].

Munji, R. N., Choe, Y., Li, G., Siegenthaler, J. A., and Pleasure, S. J. (2011). Wnt signaling regulates neuronal differentiation of cortical intermediate progenitors. *J. Neurosci.* 31, 1676–1687. doi: 10.1523/JNEUROSCI.5404-10.2011

Noctor, S. C., Martínez-Cerdeño, V., and Kriegstein, A. R. (2008). Distinct behaviors of neural stem and progenitor cells underlie cortical neurogenesis. *J. Comp. Neurol.* 508, 28–44. doi: 10.1002/cne.21669

Nomura, T., Gotoh, H., and Ono, K. (2013). Changes in the regulation of cortical neurogenesis contribute to encephalization during amniote brain evolution. *Nat. Commun.* 4, 2206. doi: 10.1038/ncomms3206

Nomura, T., Hattori, M., and Osumi, N. (2009). Reelin, radial fibers and cortical evolution: insights from comparative analysis of the mammalian and avian telencephalon. *Dev. Growth Differ.* 51, 287–297. doi: 10.1111/j.1440-169X.2008.01073.x

Nomura, T., Murakami, Y., Gotoh, H., and Ono, K. (2014). Reconstruction of ancestral brains: exploring the evolutionary process of encephalization in amniotes. *Neurosci. Res.* 86, 25–36. doi: 10.1016/j.neures.2014.03.004

Nomura, T., Takahashi, M., Hara, Y., and Osumi, N. (2008). Patterns of neurogenesis and amplitude of Reelin expression are essential for making a mammalian-type cortex. *PLoS ONE* 3:e1454. doi: 10.1371/journal.pone.0001454

Ohkubo, Y., Uchida, A. O., Shin, D., Partanen, J., and Vaccarino, F. M. (2004). Fibroblast growth factor receptor 1 is required for the proliferation of hippocampal progenitor cells and for hippocampal growth in mouse. *J. Neurosci.* 24, 6057–6069. doi: 10.1523/JNEUROSCI.1140-04.2004

O'Leary, D. D. M., Chou, S.-J., and Sahara, S. (2007). Area patterning of the mammalian cortex. *Neuron* 56, 252–269. doi: 10.1016/j.neuron.2007.10.010

O'Leary, D. D., and Sahara, S. (2008). Genetic regulation of arealization of the neocortex. *Curr. Opin. Neurobiol.* 18, 90–100. doi: 10.1016/j.conb.2008.05.011

Parent, A., and Olivier, A. (1970). Comparative histochemical study of the corpus striatum. *J. Hirnforsch.* 12, 73–81.

Piñon, M. C., Tuoc, T. C., Ashery-Padan, R., Molnár, Z., and Stoykova, A. (2008). Altered molecular regionalization and normal thalamocortical connections in cortex-specific Pax6 knock-out mice. *J. Neurosci.* 28, 8724–8734. doi: 10.1523/JNEUROSCI.2565-08.2008

Poluch, S., and Juliano, S. L. (2015). Fine-tuning of neurogenesis is essential for the evolutionary expansion of the cerebral cortex. *Cereb. Cortex* 25, 346–364. doi: 10.1093/cercor/bht232

Pownall, M. E., and Isaacs, H. V. (2010). *FGF Signalling in Vertebrate Development*. San Rafael, CA: Morgan & Claypool Life Sciences.

Puelles, L. (2001). Thoughts on the development, structure and evolution of the mammalian and avian telencephalic pallium. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1583–1598. doi: 10.1098/rstb.2001.0973

Puelles, L., Kuwana, E., Puelles, E., Bulfone, A., Shimamura, K., Keleher, J., et al. (2000). Pallial and subpallial derivatives in the embryonic chick and mouse telencephalon, traced by the expression of the genes Dlx-2, Emx-1, Nkx-2.1, Pax-6, and Tbr-1. *J. Comp. Neurol.* 424, 409–438. doi: 10.1002/1096-9861(20000828)424:3<409::AID-CNE3>3.0.CO;2-7

Rakic, P. (2009). Evolution of the neocortex: a perspective from developmental biology. *Nat. Rev. Neurosci.* 10, 724–735. doi: 10.1038/nrn2719

Reep, R. L., Finlay, B. L., and Darlington, R. B. (2007). The limbic system in Mammalian brain evolution. *Brain Behav. Evol.* 70, 57–70. doi: 10.1159/000101491

Reiner, A. (1991). A comparison of neurotransmitter-specific and neuropeptide specific neuronal cell types present in the dorsal cortex of reptiles with those present in the isocortex of mammals. *Brain Behav. Evol.* 38, 53–91.

Rowe, T. B., and Shepherd, G. M. (2015). The role of ortho-retronasal olfaction in mammalian cortical evolution. *J. Comp. Neurol.* doi: 10.1002/cne.23802. [Epub ahead of print].

Roy, A., Gonzalez-Gomez, M., Pierani, A., Meyer, G., and Tole, S. (2014). Lhx2 regulates the development of the forebrain hem system. *Cereb. Cortex* 24, 1361–1372. doi: 10.1093/cercor/bhs421

Rubenstein, J. L. (2011). Annual research review: development of the cerebral cortex: implications for neurodevelopmental disorders. *J. Child Psychol. Psychiatry* 52, 339–355. doi: 10.1111/j.1469-7610.2010.02307.x

Sansom, S. N., Griffiths, D. S., Faedo, A., Kleinjan, D. J., Ruan, Y., Smith, J., et al. (2009). The level of the transcription factor Pax6 is essential for controlling the balance between neural stem cell self-renewal and neurogenesis. *PLoS Genet.* 5:e1000511. doi: 10.1371/journal.pgen.1000511

Schlosser, G. (2005). Evolutionary origins of vertebrate placodes: insights from developmental studies and from comparisons with other deuterostomes. *J. Exp. Zool. B Mol. Dev. Evol.* 304, 347–399. doi: 10.1002/jez.b.21055

Shanmugalingam, S., Houart, C., Picker, A., Reifers, F., Macdonald, R., Barth, A., et al. (2000). Ace/Fgf8 is required for forebrain commissure formation and patterning of the telencephalon. *Development* 127, 2549–2561.

Shimamura, K., and Rubenstein, J. (1997). Inductive interactions direct early regionalization of the mouse forebrain. *Development* 124, 2709–2718.

Shimogori, T., Banuchi, V., Ng, H. Y., Strauss, J. B., and Grove, E. A. (2004). Embryonic signaling centers expressing BMP, WNT and FGF proteins interact to pattern the cerebral cortex. *Development* 131, 5639–5647. doi: 10.1242/dev.01428

Striedter, G. F. (1997). The telencephalon of tetrapods in evolution. *Brain Behav. Evol.* 49, 179–213. doi: 10.1159/000112991

Striedter, G. F. (2015). Evolution of the hippocampus in reptiles and birds. *J. Comp. Neurol.* doi: 10.1002/cne.23803. [Epub ahead of print].

Striedter, G. F., and Northcutt, R. G. (1991). Biological hierarchies and the concept of homology. *Brain Behav. Evol.* 38, 177–189. doi: 10.1159/000114387

Suárez, R., Gobius, I., and Richards, L. J. (2014). Evolution and development of interhemispheric connections in the vertebrate forebrain. *Front. Hum. Neurosci.* 8:497. doi: 10.3389/fnhum.2014.00497

Subramanian, L., Remedios, R., Shetty, A., and Tole, S. (2009). Signals from the edges: the cortical hem and antihem in telencephalic development. *Semin. Cell Dev. Biol.* 20, 712–718. doi: 10.1016/j.semcdb.2009.04.001

Sugahara, F., Aota, S. I., Kuraku, S., Murakami, Y., Takio-Ogawa, Y., Hirano, S., et al. (2011). Involvement of Hedgehog and FGF signalling in the lamprey telencephalon: evolution of regionalization and dorsoventral patterning of the vertebrate forebrain. *Development* 138, 1217–1226. doi: 10.1242/dev.x059360

Sur, M., and Rubenstein, J. L. R. (2005). Patterning and plasticity of the cerebral cortex. *Science* 310, 805–810. doi: 10.1126/science.1112070

Suzuki, I. K., Kawasaki, T., Gojobori, T., and Hirata, T. (2012). The temporal sequence of the mammalian neocortical neurogenetic program drives mediolateral pattern in the chick pallium. *Dev. Cell* 22, 863–870. doi: 10.1016/j.devcel.2012.01.004

Tarabykin, V., Stoykova, A., Usman, N., and Gruss, P. (2001). Cortical upper layer neurons derive from the subventricular zone as indicated by Svet1 gene expression. *Development* 128, 1983–1993. doi: 10.1038/ng1096-218

Toyoda, R., Assimacopoulos, S., Wilcoxon, J., Taylor, A., Feldman, P., Suzuki-Hirano, A., et al. (2010). FGF8 acts as a classic diffusible morphogen to pattern the neocortex. *Development* 137, 3439–3448. doi: 10.1242/dev.055392

Tuoc, T. C., Radyushkin, K., Tonchev, A. B., Piñon, M. C., Ashery-Padan, R., Molnár, Z., et al. (2009). Selective cortical layering abnormalities and behavioral deficits in cortex-specific Pax6 knock-out mice. *J. Neurosci.* 29, 8335–8349. doi: 10.1523/JNEUROSCI.5669-08.2009

Vasistha, N. A., García-Moreno, F., Arora, S., Cheung, A. F. P., Arnold, S. J., Robertson, E. J., et al. (2014). Cortical and clonal contribution of Tbr2 expressing progenitors in the developing mouse brain. *Cereb. Cortex* 25, 3290–3302. doi: 10.1093/cercor/bhu125

Vied, C. M., Freudenberg, F., Wang, Y., Raposo, A. A. S. F., Feng, D., and Nowakowski, R. S. (2014). A multi-resource data integration approach: identification of candidate genes regulating cell proliferation during neocortical development. *Front. Neurosci.* 8:257. doi: 10.3389/fnins.2014.00257

Wang, Y., Brzozowska-Prechtl, A., and Karten, H. J. (2010). Laminar and columnar auditory cortex in avian brain. *Proc. Natl. Acad. Sci. U.S.A.* 107, 12676–12681. doi: 10.1073/pnas.1006645107

Ypsilanti, A. R., and Rubenstein, J. L. (2015). Transcriptional and epigenetic mechanisms of early cortical development: An examination of how Pax6 coordinates cortical development. *J. Comp. Neurol.* doi: 10.1002/cne.23866. [Epub ahead of print].

Zhou, C. J., Borello, U., Rubenstein, J. L. R., and Pleasure, S. J. (2006). Neuronal production and precursor proliferation defects in the neocortex of mice with loss of function in the canonical Wnt signaling pathway. *Neuroscience* 142, 1119–1131. doi: 10.1016/j.neuroscience.2006.07.007

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

HYPOTHESIS AND THEORY
published: 12 May 2015
doi: 10.3389/fnins.2015.00162

A hypothesis for the evolution of the upper layers of the neocortex through co-option of the olfactory cortex developmental program

Federico Luzzati[1,2]*

[1] Department of Life Sciences and Systems Biology (DBIOS), University of Turin, Turin, Italy, [2] Neuroscience Institute Cavalieri Ottolenghi, Orbassano, Truin, Italy

The neocortex is unique to mammals and its evolutionary origin is still highly debated. The neocortex is generated by the dorsal pallium ventricular zone, a germinative domain that in reptiles give rise to the dorsal cortex. Whether this latter allocortical structure contains homologs of all neocortical cell types it is unclear. Recently we described a population of DCX+/Tbr1+ cells that is specifically associated with the layer II of higher order areas of both the neocortex and of the more evolutionary conserved piriform cortex. In a reptile similar cells are present in the layer II of the olfactory cortex and the DVR but not in the dorsal cortex. These data are consistent with the proposal that the reptilian dorsal cortex is homologous only to the deep layers of the neocortex while the upper layers are a mammalian innovation. Based on our observations we extended these ideas by hypothesizing that this innovation was obtained by co-opting a lateral and/or ventral pallium developmental program. Interestingly, an analysis in the Allen brain atlas revealed a striking similarity in gene expression between neocortical layers II/III and piriform cortex. We thus propose a model in which the early neocortical column originated by the superposition of the lateral olfactory and dorsal cortex. This model is consistent with the fossil record and may account not only for the topological position of the neocortex, but also for its basic cytoarchitectural and hodological features. This idea is also consistent with previous hypotheses that the peri-allocortex represents the more ancient neocortical part. The great advances in deciphering the molecular logic of the amniote pallium developmental programs will hopefully enable to directly test our hypotheses in the next future.

Keywords: neocortex evolution, piriform cortex, pallium, upper layers, cell type homology, spatial patterning, temporal patterning, doublecortin

OPEN ACCESS

Edited by:
Francisco Aboitiz, Pontificia Universidad Catolica de Chile, Chile

Reviewed by:
Loreta Medina, Universidad de Lleida, Spain
Gordon M. Shepherd, Yale University School of Medicine, USA
Fernando Garcia-Moreno, University of Oxford, UK

***Correspondence:**
Federico Luzzati, Department of Life Sciences and Systems Biology (DBIOS), University of Turin, Via Accademia Albertina 13, 10123 Turin, Italy
federico.luzzati@unito.it

Specialty section:
This article was submitted to Evolutionary Psychology and Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *01 January 2015*
Accepted: *20 April 2015*
Published: *12 May 2015*

Citation:
Luzzati F (2015) A hypothesis for the evolution of the upper layers of the neocortex through co-option of the olfactory cortex developmental program. Front. Neurosci. 9:162. doi: 10.3389/fnins.2015.00162

Introduction

The Neocortex is a pallial structure that is divided in multiple sub-regions and is made by six layers of distinct neuronal types. Despite more than a century of intense research and speculation, the evolutionary origin of this brain region is still unclear (Reiner, 2000; Butler et al., 2011; Aboitiz and Zamorano, 2013; Medina et al., 2013). Early work of Karten identified neuronal types in the hyperpallium/dorsal cortex and dorsal ventricular ridge (DVR) of sauropsids that

show patterns of connections similar to neurons of the mammalian neocortex (Karten, 1969, 2013; Butler, 1994). In particular the hyperpallium/dorsal cortex has been shown to receive visual and somatosensory information from lemno-thalamic nuclei and may thus be homologous to the visual and somatosensory cortex of mammals, while the DVR receive collo-thalamic auditory and visual projections and may be homologous to regions receiving similar projections in the temporal neocortex (Karten, 1969, 2013; Desan, 1984; Butler, 1994; Butler et al., 2011).

Nonetheless, subsequent work showed that during early development pallial progenitors of all tetrapods are regionalized into at least four conserved domains, referred as medial (MP), dorsal (DP), lateral (LP), and ventral (VP) pallium, that give rise to distinct radially migrating glutamatergic neurons (Fernandez et al., 1998; Puelles et al., 2000; Brox et al., 2004). The neocortex is generated by DP progenitors that in sauropsids give rise only to the hyperpallium (in birds) and the dorsal cortex (in reptiles; **Figure 1A**). By contrast the DVR is generated by LP and VP progenitors that in mammals give rise to claustro-amygdalar nuclei together with structurally and functionally conserved regions receiving olfactory and pheromonal information (olfactory cortex and cortical/medial amygdala respectively). These studies strongly suggests that the neocortex is homologous, as a field, only to the hyperpallium/dorsal cortex while the DVR is homologous to the amygdala, that also receives auditory and collo-thalamic visual projections, the claustrum and the entopeduncular nucleus (Bruce and Neary, 1995; Striedter, 1997; Puelles et al., 2000; Puelles, 2001; Butler and Molnár, 2002; Bruce, 2007; Medina et al., 2013).

Organization of Dorsal Pallial Derivatives in Mammals and Reptiles

It is generally accepted that in the reptilian ancestor of mammals the medial, dorsal and lateral cortices were laminated but were made only by three layers, an organization that is also called allocortex (**Figure 1B**; Nieuwenhuys, 1994; Reiner, 2000; Shepherd, 2011; Fournier et al., 2015). In mammals, this type of cortex is still present in two structurally and functionally well

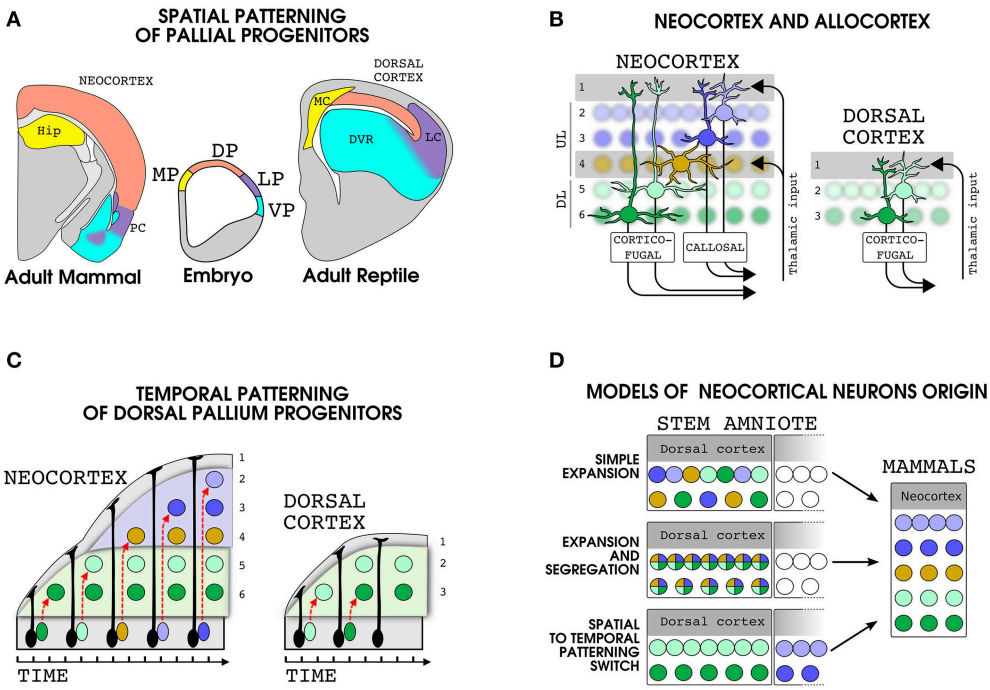


FIGURE 1 | Development and evolution of dorsal pallial derivatives in amniotes. (A) Spatial patterning mechanisms subdivide the embryonic pallial progenitors in at least four domains: Medial pallium (MP, yellow), dorsal pallium (DP, pink), lateral pallium (LP, violet) and ventral pallium (VP, cyan). The brain regions produced by each domain are shown in a mammal (left) and a reptile (right) with the same color code. **(B)** Schematic representation of the organization of the cellular layers and main input and output projections in the neocortex (left) and in the reptilian dorsal cortex (right). **(C)** Development of dorsal pallium glutamatergic neurons in mammals and reptiles. In the neocortex the same progenitor produces multiple cell types in an inside-out sequence. In the reptilian dorsal cortex, the dorsal pallium progenitors produce a reduced number of cells in an outside-in sequence. The migration of immature neuroblasts is indicated by a dashed red arrows. Please note that, along with our theory, in **(B,C)** we used the same color code for the mammalian DL and reptilian dorsal cortex neurons. Nonetheless, it is important to note that the precise correspondence between layer II and III neurons of the dorsal cortex and layer V and VI of the neocortex is not known. **(D)** Models of the evolution of the principal neurons of the neocortex. Each color represent a set of gene modules specifying a particular neuronal types in the modern neocortex (right). Three different possibile pattern of expression of these gene modules in cells of the dorsal cortex of the stem amniote are shown (left). Abbreviations: HIP, hippocampus; MC, medial cortec; LC, lateral cortex; PC, piriform cortex.

conserved regions that border the neocortex: the hippocampus, a MP derivative, and the piriform cortex, a LP derivative that receive a direct input from the olfactory bulb. In the allocortex the more superficial layer I is a plexiform layer where extrinsic and intrinsic projections meet the apical dendrites of pyramidal neurons whose cell bodies settle in layers II and III (Haberly, 1990; Ulinsky, 1990). In general, the cellular density is higher in layer II than in layer III particularly in the piriform/lateral cortex and the hippocampus. The neocortex shares with allocortex the basic microcircuits, but it stands out for the higher number of neurons and layers (Shepherd, 2011; Fournier et al., 2015). In many respects the neocortex can be described as a double allocortex, with two couples of pyramidal layers, namely upper (II,III,IV; UL) and deeper (V,VI, DL), each below a plexiform layer carrying extrinsic inputs, namely layer I and IV (**Figure 1B**; Shepherd, 2011). In primary sensory areas the layer IV is enriched in stellate cells, a glutamatergic cell type that lack apical tufts and output projections and is specialized in receiving thalamic inputs (Sanides, 1969; Jones, 1975). By contrast, most of the glutamatergic neurons in the other layers possess an apical dendrite directed to layer I and output connections emerging at the opposite pole of the cell body (**Figure 1B**). The UL neurons axons are mainly involved in cortico-cortical connectivity and include homotopic and heterotopic callosal projections to the contralateral hemisphere, while DL neurons target various subcortical structures (**Figure 1B**; Shepherd, 2011; Greig et al., 2013). To understand the evolution of the neocortex we should thus first disclose the developmental mechanisms that triggered the multiplication of cellular and plexiform layers. As expected, comparative studies shows that in respect to reptiles, the mammalian DP progenitors have an increased proliferation (Nomura et al., 2013, 2014) that include the appearance of a well defined layer of intermediate progenitor cells: the SVZ (Martínez-Cerdeño et al., 2006; Abdel-Mannan et al., 2008; Cheung et al., 2010). In mammals, this increase in cell proliferation is accompanied by a distinct pattern of migration of neuroblasts that passes older cells (n.b. in both piriform cortex and neocortex; Bayer, 1986) rather than accumulating below them as in reptiles (Goffinet et al., 1986; **Figure 1C**). Since cortical neurons are generally considered to be already committed to a specific cell type at their birth (Greig et al., 2013; Rouaux and Arlotta, 2013), a major point to understand the emergence of the neocortex will be to unravel the evolution of the developmental program set up by dorsal pallium progenitors and regulating the production of neocortical glutamatergic neurons.

Models of Transition from a Three to a Six Layered Cortex

The study of the organization of genes underlying cell identity suggests that genes sub-serving specific functions can be grouped into modules whose expression is regulated by a limited number of transcription factors also called "selector genes" (Arendt, 2008; Achim and Arendt, 2014). In this model, during development morphogens regulate patterning by inducing the expression of the selector genes at specific times and place. Starting from these considerations, three major mechanisms have been recently proposed to underlie the evolution of new cell types from a precursor cell in a given lineage: (1) *Divergence of functions*, in which two sister cell types inherit the same gene modules and gradually modify them with time, (2) *Segregation of functions*, in which two sister cell types lose complementary parts of the gene modules of the former precursor cells. (3) *Co-option of functions*, in which the precursor cell co-opts the gene modules of an unrelated cell type (Arendt, 2008; Achim and Arendt, 2014). It is to note that the term co-option generally refers to the acquisition of new roles by pre-existing characters (True and Carroll, 2002). In the specific case of the gene regulatory networks controlling cell type specification, co-option may occur for cis- and trans- acting transcriptional regulators at multiple levels and can thus be involved in all the presented modes of cell type evolution. Nonetheless, for the *co-option of functions* hypothesis these mechanisms should act at the level of selector genes, thus leading to the ectopic expression of the pre-existent gene regulatory networks of complex developmental programs. This latter possibility has been proposed to explain multiple evolutionary innovations such as the evolution of novel sex determining genes (Sutton et al., 2011; Takehana et al., 2014) or the acquisition of a chondrogenic fate in the neural crest lineage (Meulemans and Bronner-Fraser, 2007; Hall and Gillis, 2013).

The specification of neocortical neurons depends on spatial patterning events delimiting the DP progenitors (**Figure 1A**; see for review Puelles, 2011), followed by temporal patterning mechanisms that lead these cells to sequentially produce the DL (first) and UL (last) (**Figure 1C**; Angevine and Sidman, 1961; Greig et al., 2013; Gao et al., 2014). When applying the above mentioned concepts to the evolution of the neocortical neurons, three main hypotheses can be drawn (**Figure 1D**): (1) *Simple Expansion*: DP progenitors of the reptilian ancestors produced homologous of both UL and DL neocortical neurons following the same temporal patterning mechanisms as in the modern neocortex. In this model the emergence of the neocortex was driven by changes only in the proliferation of DP progenitors and migration of their daughter cells. (2) *Expansion and Segregation*: gene modules underlying specific functions of UL and DL were present in a single precursor cell in the ancestral DP derivatives and became segregated and subsequently refined in distinct sister cell types. In this case the temporal patterning of DP progenitors will be a mammalian innovation. (3) *Spatial to Temporal patterning switch*: DP progenitors co-opted the expression of gene modules specifying the neuronal types of other pallial regions (i.e., MP, VP or LP), thus leading to the appearance of new cell types in the DP derivatives. The temporal patterning of neocortical progenitors may thus represent a patchwork of formerly spatially segregated developmental programs. In this case part of the neocortical cells may have a sister cell type in a different pallial domain.

Some evidences against the first two hypotheses were first presented by Ebner based on hodological considerations (Ebner, 1976). Indeed, reptilian dorsal cortex neurons have projections to subcortical targets that resemble those of neocortical DL neurons but lack the extensive network of intracortical connections, including homotopic contralateral projections, that are typical

of UL neurons (Ebner, 1976; Desan, 1984; Hoogland and Vermeulen-Vanderzee, 1989). Thus, Ebner proposed that the UL neurons may represent an evolutionary novelty. In the early'90 Anton Reiner extended Ebner hypotheses by showing that UL specific interneurons are lacking from the reptilian dorsal cortex (Reiner, 1991, 1993). However, later studies showed that interneurons are generated in the sub-pallium (Cobos et al., 2001; Wichterle et al., 2001) and this makes the Reneir's observations only indirectly related to the DP progenitors developmental program. In 2009 we described a specific population of neurons of the layer II of the neocortex that according with Ebner and Reiner ideas was absent from the dorsal cortex of *Lacerta Muralis*, a lizard. However, virtually identical cell types were observed in the LP and VP derivatives of both lizard and mammals thus supporting the spatial to temporal patterning switch hypothesis (Luzzati et al., 2009). The interest about these cells comes from the fact that (1) they express Tbr1, suggesting a pallial origin, and (2) morphological and distributive features support that they represent a specific neuronal population that is shared by different pallial derivatives and tetrapod species. In the following sections we will describe and discuss in detail our observations in the context of more recent data that further support these hypotheses.

Old Cells in New Layers: The Strange Case of the DCX+ Cells in the Layer II of Different Amniote Pallial Derivatives

Doublecortin (DCX) is a microtubule associated protein involved in cytoskeletal dynamics during migration and differentiation of immature neurons (Francis et al., 1999; Gleeson et al., 1999; Friocourt, 2003). Accordingly, in the adult brain the expression of DCX is restricted to regions of ongoing neurogenesis (Nacher et al., 2001; Brown et al., 2003; Couillard-Despres et al., 2005; Luzzati et al., 2006; Balthazart and Ball, 2014). The only clear exception to this rule is a population of neurons in the layer II of the piriform cortex and neocortex (Gómez-Climent et al., 2008; Luzzati et al., 2009) that are not adult generated but show a strong and homogeneous DCX immunoreactivity that closely resembles that of immature neurons. Layer II DCX+ cells occurs in two main morphological subtypes: Type I cells have small cell bodies and dendrites confined to layer II, while type II cells have larger cell bodies and send one or two dendritic branches to layer I (Luzzati et al., 2009). Electrophysiological analyses in DCX-GFP mice piriform cortex revealed that type I cells resemble immature neurons, while most type II cells shows mature features with large Na+ currents and multiple action potentials (Klempin et al., 2011). In both piriform cortex and neocortex type I and II DCX+ cells express Tbr1 suggesting that they are glutamatergic neurons derived from pallial germinative zones (Englund et al., 2005; Hevner et al., 2006; Luzzati et al., 2009). Interestingly the clear predominance of subpial dendrites over basal dendrites place type II cells within the population of atypical pyramidal cells previously defined as "extraverted neurons" (Sanides and Sanides, 1972). Since the lack of basal dendrites represent an ancient feature in the evolution of pyramidal cells, extraverted neurons in the neocortex were originally considered a conserved cell type. Besides laboratory mice and rats (Nacher et al., 2001; Luzzati et al., 2009), in which layer II DCX+ cells are scarce and mostly restricted to the piriform and perirhinal cortices (Nacher et al., 2001), in all other mammalian species analyzed so far such as rabbits (Luzzati et al., 2009), guinea pigs (Xiong et al., 2008; Luzzati et al., 2009), cats (Cai et al., 2009), dogs (De Nevi et al., 2013), giant african mole rats (Olude et al., 2014), epaulatted fruit bats (Gatome et al., 2010), reshus macaques (Cai et al., 2009; Fung et al., 2011), and humans (Cai et al., 2009), DCX+ cells in layer II are abundant and widely distributed in both piriform cortex and neocortex. A detailed analysis of the distribution of these cells in rabbits and guinea pigs revealed that layer II DCX+ cells are specifically associated to the network of brain regions connected to the lateral entorinal cortex (LEC; **Figure 2A**; Luzzati et al., 2009). These brain regions, including the rostro-lateral neocortex and piriform cortex, receive information about local sensory objects and have been implicated in non-spatial cognition. By contrast caudo-medial neocortical areas connected to the Medial EC (MEC) and processing information of both external and internal stimuli involved in spatial cognition, are mostly negative for DCX (for anatomical and functional descriptions of LEC and MEC connections see Burwell and Amaral, 1998a,b; Jones and Witter, 2007; Knierim et al., 2014). Within LEC connected networks the DCX+ cells show a strong preferential distribution in higher order areas such as posterior piriform cortex, secondary sensory areas, insular, perirhinal cortex and prefrontal cortex (**Figure 2A**). Altogether, the similarities in the morphology, laminar position and preferential distribution in higher order areas strongly suggests that DCX+ cells of the neocortex and piriform cortex may represent a common cell type that is shared by these two regions.

Notably, in the lizard *L. Muralis* we identified DCX+/Tbr1+ cells morphologically similar to those of mammals in the layer II of the olfactory cortex and DVR, with a preferential distribution in higher order areas, but not in the dorsal cortex (**Figure 2B**). When compared to the DCX+/Tbr1+ cells in the neocortex, the general distribution of these cells in the lizard was consistent with the homologies proposed by Karten (Karten, 1969; Butler et al., 2011). Indeed, the DVR has been proposed to be homologous to temporal neocortical areas, such as auditory and secondary somatosensory and visual cortices, that in mammals show high numbers of DCX+/Tbr1+ cells. By contrast, the neocortical regions proposed as homologous of the dorsal cortex, that include primary somatosensory and visual cortices as well as the posterior cingulate, retrosplenial, and postrhinal cortices, are largely devoid of DCX+/Tbr1+ cells. Collectively, these data strongly support that layer II DCX+/Tbr1+ cells represent a conserved cell type in amniotes. In addition, although the sauropsids homologs of mammalian MEC and LEC associated circuits are still poorly defined (Rattenborg and Martinez-Gonzalez, 2011; Allen and Fortin, 2013; Abellán et al., 2014), it is tempting to speculate that non-newly generated DCX+/Tbr1+ cells may be involved in a conserved form of structural plasticity selectively associated to higher order areas of non-spatial learning and memory networks in amniotes. At the same time, our data suggests that the presence of DCX+/Tbr1+ cells in

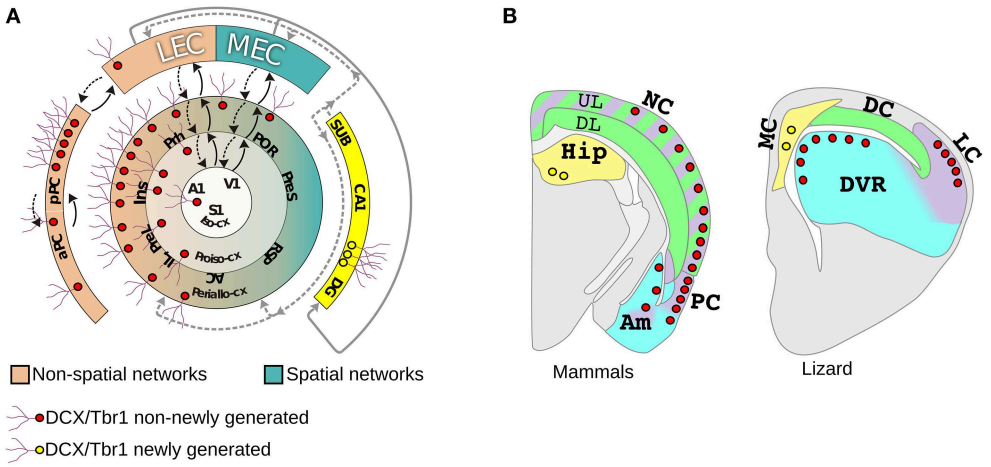


FIGURE 2 | Distribution of DCX+/Tbr1+cells in the pallium of mammals and a lizard. (A) The distribution of layer II DCX+/Tbr1+ cells either newly generated (yellow) or non-newly generated (red) is shown in a schematic view of mammalian allocortical and neocortical regions. The neocortex is schematized according to Sanides in three concentric rings: peri-allocortex, proisocortex, and isocortex. The isocortex contains the primary sensory areas from which information flows through a hierarchichal sequence of areas and reaches either the lateral (LEC) or medial enthorinal cortex (MEC). Areas connected with LEC and MEC are shown in pink and turquoise green respectively, feedforward (solid arrows) and feedback (dashed arrow) pathways are also shown. **(B)** Schematic coronal sections showing the distribution of DCX+/Tbr1+ cells in different pallial domains in mammals (left) and lizard (right). Additional abbreviations: A1, primary auditory cortex; AC, anterior cingulate cortex; DP, dorsal pallium; IL, infralimbic cortex; Ins, insular cortex; pPC posterior piriform cortex; aPC; anterior piriform cortex; PreL, prelimbic cortex; PreS, presubiculum; POR, postrhinal cortex; Prh, perirhinal cortex; RSP, retrosplenial cortex; SUB, subiculum. Redrawn from Luzzati et al. (2009).

DP derivatives may represent a mammalian innovation. This supports the hypothesis of Reiner that the UL are an evolutionary novelty, but in parallel introduces the possibility that this novelty has been produced by re-using (or co-opting) pre-existing cell types. In particular, we propose that in the transition from the stem-amniote to mammals, DP progenitors instead of exiting from the cell cycle after the production of the DL neurons homologs, continued to proliferate by setting up a LP and/or VP developmental program, giving rise to the UL of the NC. Thus, the evolution of the neocortex could be attributed to a spatial to temporal patterning switch involving DP and LP/VP developmental programs. An interesting aspect of this model is that it could reconcile the developmental data supporting the field homology of the primary progenitors, with the striking similarities existing between neurons of the neocortex and LP and VP derivatives of sauropsids. Future studies in other reptilian species will be required to understand if the distribution of DCX+/Tbr1+ cells in *L. Muralis* represents the basal reptilian condition or, as happen in mice, this species simply lack this feature. An important point will be also to define where and when these cells are generated in different tetrapod species. Indeed, previous studies have shown that the VP and LP progenitors give rise to neurons that tangentially migrate to the neocortex in mice (Puelles, 2011; Teissier et al., 2012). Most of these VP/LP derived cells have a transient existence in mice, but we cannot exclude that in other mammalian species some of these cells may persist for longer post-natal periods (Teissier et al., 2010, 2012). Finally, molecular and functional analyses will be necessary to understand if these cells in different amniote species and pallial derivatives actually represent sister cell types. Nonetheless, as we will discuss in the next paragraphs, beside this intriguing cell population the hypothesis of the co-option of the LP/VP developmental program is supported also by other anatomical and developmental data.

Similarity in Gene Expression Between PC and Neocortical Layers II/III and a Hypothesis of Their Evolutionary Relationships

According to our hypothesis, the UL neurons of the neocortex may have sister cell types in other pallial regions. To gain insight on this issue and to identify the best candidate regions whose developmental program may have been co-opted in the evolution of the UL, we performed an analysis in the *in situ* hybridization database of the Mouse Allen Brain Atlas (Lein et al., 2007). In this analysis we compared the lists of the first 500 genes that were enriched relative to the rest of the CNS (contrast structure, gray) in each of the following regions: neocortical layers II/III, layer IV, layer V/VI, piriform cortex, subiculum and cortical subplate (claustro-amygdaloid complex, and endopiriform nucleus; **Figure 3**, **Supplementary data sheet 1A**). Layer II/III is closely related to layer IV, with 352 co-expressed genes, and relatively well correlated with layer V/VI, with 250 co-expressed genes (**Table 1**, **Figure 3**, **Supplementary data sheet 1B**, Supplementary Figure 1). Surprisingly, layers II/III cells also shared about 208 enriched genes with the piriform cortex (42%; **Table 1**, **Figures 3**, **4**, Supplementary Figure 1). The layers V/VI were less related to

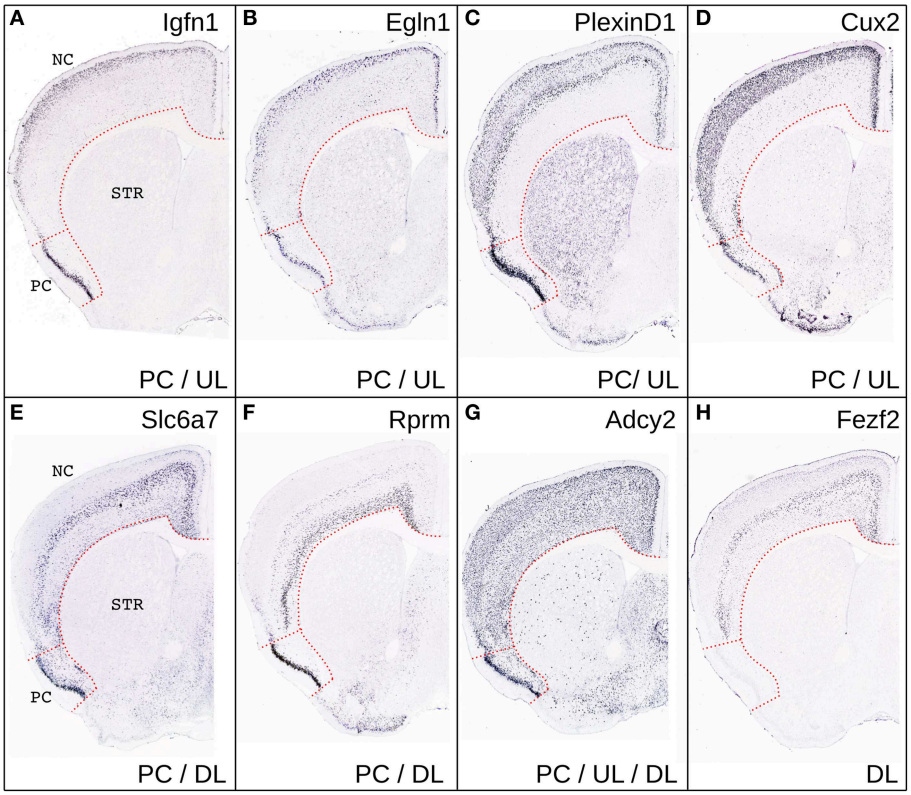


FIGURE 3 | Comparison of gene expression in PC and NC. Representative coronal sections from the Allen Brain Atlas showing the expression of few representative genes selectively enriched in the UL and PC **(A–D)**, in DL and PC **(E,F)** in DL, UL and PC **(G)** or only in DL **(H)**. Please note that CUX2, was not present in the list of genes enriched in PC relative to the rest of the gray matter likely because of its relatively widespread expression in the CNS.

the piriform cortex with only 143 co-expressed genes (29%; **Table 1**, **Figures 3**, **4**, Supplementary Figure 1). In addition only 41 genes were exclusively enriched in piriform cortex and layers V/VI but not in layers II/III (29% of PC and layer V/VI common genes). By contrast 106 genes were specifically enriched only in layer II/III and in piriform cortex but not in layer V/VI (51% of PC and layer II/III common genes; **Figures 3**, **4**, **Supplementary data sheet 1C**). These striking similarities in the gene expression profile raise the intriguing possibility that the developmental program that provided the base for the evolution of the neocortical layers II/III have been that of the olfactory cortex.

This idea is not new and dates back to the beginning of twentieth century. Indeed, early neuroanatomist proposed that a primordium of the neocortex may be found in the superposition of lateral and dorsal cortex, the so called *superpositio lateralis* (**Figure 5**; Kappers and Theunissen, 1908; Kappers, 1909; De Lange, 1911; Schepers, 1948). This superposition is observed only in some species and its extension correlates with the development of the olfactory system (Ulinsky, 1990). Given that most of the increased encephalization of the first mammaliaformes was due to a huge expansion of the olfactory bulbs and olfactory cortex (Rowe et al., 2011), a substantial development of the lateral superposition could have been present in these species and

TABLE 1 | Percentage of shared genes among the first 500 genes enriched in each of the indicated pallial sub-regions.

Percentage of gene co-expression in different pallial regions						
	PC	**NC II/III**	**NC IV**	**NC V/VI**	**C. Sub**	**Subic.**
PC		42	30	29	37	16
NC II/III	42		70	49	21	16
NC IV	30	70		51	13	11
NC V/VI	29	49	51		20	26
C. Sub	37	21	13	20		38
Subic	16	16	11	26	38	

PC, Piriform cortex; NC, Neocortex; C. Sub, Cortical subplate; Subic., Subiculum.

preceded the emergence of the neocortex. In these superpositions the medial edge of the lateral cortex is located on top of the lateral edge of the dorsal cortex giving rise to a rudimentary six layered arrangement (**Figure 5A**). Indeed, this region have a dense layer II on top of a sparser layer III that are continuous with the olfactory cortex and receive a direct projection from the olfactory bulb (Minelli, 1967; Regidor, 1977; Desan, 1984; Martinez-Garcia et al., 1991), it posses a parvo-cellular layer IV that receive thalamic inputs (Bruce and Butler, 1984; Desan, 1984; Desfilis et al., 2002) and two deep cellular layers (V and VI) that project to

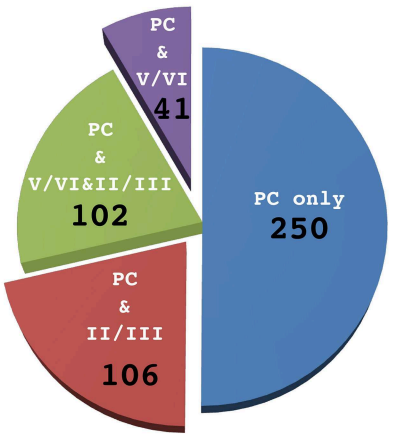


FIGURE 4 | Comparison of genes shared by piriform cortex and laiers II/III or V/VI of the neocortex. The pie chart represents the 500 genes enriched in the piriform cortex. Each sector indicate the number of genes shared only with layers V/VI (violet), only with layer II/III (red) or with both layer II/III and V/VI (green). The fraction of genes that are not enriched neither in layer II/III nor in layer V/VI are in blue.

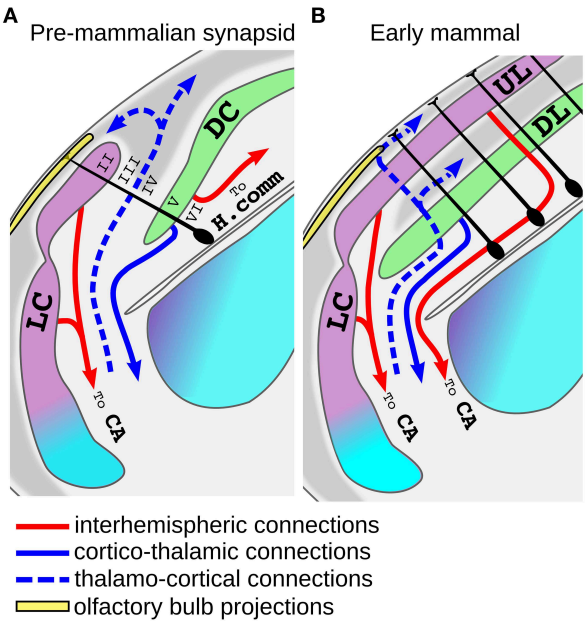


FIGURE 5 | Model for the origin of the neocortex from the superposition of lateral and dorsal cortex. (A) Schematic view of the putative organization of the dorso-lateral part of the telencephalon in an early mammaliaform (pre-mammlian synapsid). In these animals the lateral cortex (LC, violet) may have expanded over the dorsal cortex (DC, green), and at some point some radial glial progenitor (dark cells) may have started to produce both LC and DC cells. Note that since the internal anatomy of these animals is unknown, this scheme was based on modern macrosmatic reptiles. Radial glial cells of other brain regions are omitted for clarity. The proposed homology with neocortical layers is indicated with roman nueral. **(B)** Tangential expansion of the progenitors of the proto-neocortical column gave rise to the establishement of the neocortex. Note that the more lateral part of the neocortex maintains a direct olfactory input. Abbreviations: H.comm., hippocampal commissure; AC, Anterior commissure.

various subcortical targets (Minelli, 1967; Ebner, 1976; Regidor, 1977; Desan, 1984; Hoogland and Vermeulen-Vanderzee, 1989). This layer arrangement is closely reminding that of the neocortex and in particular of the lateral peri-allocortical regions (insular and perirhinal cortices; **Figure 2A**) which receive olfactory information, lacks layer IV and have a dense layer II that is continuous with the priform cortex (Sanides, 1969; Sanides and Sanides, 1972; Shipley and Geinisman, 1984; Haberly, 1990). Previous authors also highlighted the presence of numerous allocortical features in the peri-allocortical ring, and accordingly proposed that it represent the more ancestral part of the neocortex (Abbie, 1940, 1942; Sanides, 1969; Sanides and Sanides, 1972). The cytoarchitectural similarities between the lateral superposition and the neocortex include also their relationships with bordering regions. In particular, on the medial side the deeper layers of the superposition are in continuity with the non-superposed part of the dorsal cortex while DL of the neocortex are in continuity with the subiculum. An homology between the non-superposed part of the dorsal cortex and the subiculum has been previously proposed (Hoogland and Vermeulen-Vanderzee, 1989). Moreover, this latter region share many features with the DL (Ishizuka, 2001) and accordingly our analyses in the Allen Brain Atlas indicated that it has more enriched genes in common with layer V/VI than layer II/III (26 and 16%, respectively, **Table 1**, **Supplementary Figure 1**).

Another interesting aspects of the hypothesis that the neocortex derived from the superposition of lateral and dorsal cortex, is that it may account for some hodological features that the UL shares with the olfactory cortex but not with the reptilian dorsal cortex. For instance, the olfactory cortex of tetrapods possesses homotopic projections to the contralateral hemisphere passing through the anterior commissure (Zeier and Karten, 1973; Butler, 1976; Hoogland and Vermeulen-Vanderzee, 1995; Sassoè-Pognetto et al., 1995; Suárez et al., 2014). Inter-hemispheric projections arising from UL neurons still decussate exclusively through this commissure in monotreme and marsupials, and this is generally thought to represent the basal condition in mammals (Ashwell et al., 1996; Suárez et al., 2014). Nonetheless, in sauropsids inter-hemispheric connections of DP and MP derivatives decussate at the nearby pallial/hippocampal commissure (Butler, 1976; Martinez-Garcia et al., 1990; Atoji et al., 2002). Thus, our hypothesis may account for the strange evolutionary history of the inter-hemispheric connections of the mammalian DP derivatives that at first flipped their direction and coursed a long lateral trip to decussate with fibers of the olfactory cortex at the anterior commissure. Only in eutherian mammals most, but not all, of the neocortical inter-hemispheric connections turned medially again decussating at the corpus callosum (Suárez et al., 2014). Another interesting similarity between the connections of olfactory cortex and UL is that they are both the source of feed-forward projections that flow to a series of hierarchical areas progressively defining sensory

objects and ultimately converging on the LEC (Felleman and Van Essen, 1991; Haberly, 2001; Gilbert and Sigman, 2007; Wilson and Sullivan, 2011). In summary, the idea that the six layered neocortex originated from the superposition of lateral and dorsal cortex is consistent with the fossil record and may account not only for the topological position of the neocortex, but also for its basic cytoarchitecthural and hodological features. Unfortunately very little is known about the embryonic development of this putative six-layered primordium in modern reptiles. Guirado and Davila identified radial glial processes crossing both dorsal and lateral cortex in the lateral superposition of the lizard *Podarcis Hispanica* (Guirado and Dávila, 2002) and we made similar observations in Golgi stains of *Lacerta Sicula* (Luzzati unpublished observation). These authors raised the possibility that an independent progenitor domain giving rise to neurons of both dorsal and lateral cortex may actually exist in some living reptiles. In contrast to this interpretation however, Ulinsky reported that during development the layer II of the reptilian dorsal and lateral cortex is a continuous stratum of cells that is secondarily ruptured during differentiation (Ulinsky, 1990). Starting from this latter observation, a possible scenario for the evolution of the neocortex may be that in early mammaliaforms the homologs of UL and DL cells organized in a proto-neocortical column that was initially produced by spatially segregated progenitors. At some point a spatial to temporal patterning switch, together with the evolution of the inside-out neurogenic gradient, led to the generation of the proto-neocortical module from a single population of progenitors (**Figure 5A**). This crucial event enabled the tangential expansion of this module providing the basis for the establishment of the modern neocortex (Rakic, 1995; Lewitus et al., 2014; **Figure 5B**). According to the growth rings hypothesis of Sanides, during this tangential expansion the internal parts of the neocortical island progressively lost their allocortical features with the addition of stellate cells in layer IV and a reduction of cell density in layer II (Sanides, 1969; Sanides and Sanides, 1972). An intriguing aspect of this model is that it implies that the early neocortex worked as an higher order association cortex and that primary sensory areas appeared only subsequently. This latter idea has been also recently proposed based on functional models of both mammalian and reptilian allocortices (Fournier et al., 2015).

Several crucial questions remain regarding the emergence of the inside out-gradient of neurogenesis, the appearance of layer IV cells and the arrival of the collo-thalamic projections to the dorsal pallial derivatives.

Genetic and Developmental Data Supporting a Spatial to Temporal Patterning Switch in the Evolution of the Mammalian Neocortex

A hallmark of the evolution of the mammalian neocortex is the emergence of a SVZ in the DP (Martínez-Cerdeño et al., 2006; Cheung et al., 2010), and interestingly the intermediate progenitors (IPc) that populate this germinative layer are mainly involved in the generation of UL neurons (Tarabykin et al., 2001; Martínez-Cerdeño et al., 2006; Kowalczyk et al., 2009). Although, an SVZ is not always evident in sauropsids, studies in turtle and chick showed that putative IP like cells are present in late developmental phases of the LP and VP of turtle and chick (Martínez-Cerdeño et al., 2006; Cheung et al., 2007). The acquisition by DP progenitors of a character (the IPc) that pre-existed in LP/VP progenitors is consistent with our hypothesis. Nonetheless, the IPc step is a common feature in stem cell systems and it has been described for multiple neuronal progenitors populations in both vertebrate and invertebrate brains (Brand and Livesey, 2011). Mammalian DP progenitors may have independently increased the generation of IP to amplify neuron production. Future studies defining the role of the SVZ during pallial development will be necessary to understand the role of this germinative layer in the emergence of the neocortex. While deciphering the developmental program set up by pallial progenitors is a fundamental issue, recent studies also tried to extend previous inter-species comparisons of pallial neuronal types with more modern molecular techniques. The comparison of the chick and mouse transcriptomes of telencephalic regions with either disputed or undisputed homology (Belgard et al., 2013) revealed significant similarities for the hippocampus but failed to identify specific relationships between any other pallial region. The only exception was a weak correlation between the neocortical layer IV and a thalamorecipient field of the nidopallium (a VP derivative). Along with our hypothesis for the evolution of layer II/III it would be interesting to evaluate whether the appearance of stellate cells in layer IV was due to the co-option of the developmental program of the thalamo-recipient VP cells. Unfortunately the olfactory cortex was not analyzed in this study, probably because it is highly reduced in chick. These transcriptomes comparisons supported the view that DP and VP derivatives underwent dramatic changes in morphology and function during amniote evolution (Montiel and Molnár, 2013). At the same time, although such analyses can make a strong case for homology, negative results are more difficult to interpret. Huge differences in the transcriptome do not rule out the occurrence of homologous cell types that greatly changed their relative proportions or mixed with novel cell types. This further indicates the importance of defining the evolutionary history of individual pallial cell types (the so called cell type homology or deep-homology; Arendt, 2008; Shubin et al., 2009) to understand the divergence of DP derivatives in amniotes.

In this perspective, in the last years different authors have analyzed the pattern of expression of the sauropsid orthologs of genes expressed in specific neocortical layers (Nomura et al., 2008, 2013; Dugas-Ford et al., 2012; Suzuki et al., 2012; Chen et al., 2013; Suzuki and Hirata, 2014). The drawback of this approach is that the few individual genes that have been analyzed are expressed by multiple cell types not only in the neocortex but also in other brain regions (Medina et al., 2013). Moreover, the layer specificity of some of the markers of upper layer cells have been disputed (Dugas-Ford et al., 2012). Nonetheless, from these studies a general pattern emerged in which the orthologs of DL markers tend to be expressed more medially than those of the UL. These latter genes are mostly expressed in LP derivatives

such as the mesopallium/pallial thickening or the olfactory cortex (Dugas-Ford et al., 2012; Suzuki and Hirata, 2013; Nomura et al., 2014). Since clonal analyses in chick indicate that pallial neurons expressing the orthologs of DL and UL markers are produced by spatially segregated progenitors (Suzuki et al., 2012), these observations are consistent with the hypothesis that the evolution of the mammalian neocortex involved a spatial to temporal patterning switch (Dugas-Ford et al., 2012; Suzuki and Hirata, 2013; Nomura et al., 2014).

Surprisingly, early dorso-medial and dorso-lateral progenitors of the chick pallium were able to sequentially produce cells expressing DL and UL markers *in vitro* (Suzuki et al., 2012). Caution should be made in the interpretation of these data, first because the authors did not verified the purity of the explanted regions and second because the expression of few marker is a very weak evidence that chick and neocortical progenitors generates the same cell types.

Nonetheless, these results introduce the intriguing possibility that an intrinsic temporal patterning mechanism specifying pallio-fugal, thalamo-recipient, and pallio-pallial neuronal types was present in pallial progenitors of the common ancestor of all amniotes or even vertebrates. This idea would be consistent with the fact that temporal patterning of primary progenitors is a major mechanism for generating neuronal diversity in Drosophila (Li et al., 2013a,b; Eroglu et al., 2014). At some point in vertebrate evolution, spatial patterning cues may have differentially repressed specific parts of this program along medio-lateral and anterior-posterior axes. The molecular mechanism that led to the evolution of the six-layered neocortex could thus be a de-repression of the ancestral developmental program in DP progenitors or a subpopulation of them. A similar idea has also been proposed by Luis Puelles to explain the stratified birth dates of VP derived neurons migrating to the neocortex (Puelles, 2011): "One wonders whether this implies a normally repressed, cryptic 6-layer potency existing throughout the pallium, which is simply de-repressed and thus allowed to emerge at the neocortex." Interestingly, the transcription factor zbtb20 has been recently shown to play a general repressive activity over the specification of neocortical cell types of both UL and DL (Nielsen et al., 2014). In the mammalian pallium, this transcription factor is expressed in MP, LP, and VP but not DP regions and gain and loss of functions have been shown to shift the neocortical limit, at least medially (Nielsen et al., 2007, 2014; Rosenthal et al., 2012). Detailed comparative analyses will be necessary to understand if down-regulation of zbtb20 or other transcriptional repressors in DP progenitors may have played a role in the evolution of the neocortex.

In conclusion, our understanding of the genetic logic of cell type specification in the neocortex and other pallial regions of amniotes is constantly growing and this will likely enable to test current theories of the evolution of the mammalian pallium. These analyses would be greatly helped by the comparison of the genetic fingerprint of more restricted cell populations and the layer II DCX+/Tbr1+ cells represent an attractive candidate for such analyses.

Acknowledgments

I'd like to thank Paolo Peretto for critical readings and comments to the manuscript and Luis Puelles and Aldo Fasolo for useful discussions on the initial version of this theory. I would also like to thank Aldo Fasolo and Maria Fosca Franzoni for the golgi slides of *Lacerta Sicula*. This work is dedicated to the memory of Prof. Aldo Fasolo and Prof. Maria Fosca Franzoni. This work was supported by Progetti di Ricerca di Interesse Nazionale (PRIN)-Peretto 2010-2011; and by Luzzati-Ricerca Locale 2013.

Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnins.2015.00162/abstract

Supplementary data sheet 1 | Gene expression comparisons between different pallial regions of the mouse brain. (A) List of the first 500 genes enriched in neocortical layer II/III, neocortical layer IV, neocortical layer V/VI, piriform cortex, cortical subplate, and subiculum in respect to the rest of the gray matter (contrast structure gray). For each gene the fold change in respect to gray matter calculated by the allen brain atlas is indicated. **(B)** Percentage of sharing, number and lists of genes shared by the selected pallial regions. **(C)** Number and Lists of genes selectively shared by Piriform cortex (PC) and neocortical layers V/VI and by PC and neocortical layers II/III. For each gene a manually evaluated estimate of the level of preferential labeling is indicated by crosses ranging from 0 (low specificity) to 4 (high specificity). A color code is additionally used to indicate high specificity (yellow) medium to low specificity (pink) or absence of any evident specificity (blue).

References

Abbie, A. A. (1940). Cortical lamination in the Monotremata. *J. Comp. Neurol.* 72, 429–467. doi: 10.1002/cne.900720302

Abbie, A. A. (1942). Cortical lamination in a polyprotodont marsupial, *Perameles nasuta*. *J. Comp. Neurol.* 76, 509–536. doi: 10.1002/cne.900760310

Abdel-Mannan, O., Cheung, A. F. P., and Molnár, Z. (2008). Evolution of cortical neurogenesis. *Brain Res. Bull.* 75, 398–404. doi: 10.1016/j.brainresbull.2007.10.047

Abellán, A., Desfilis, E., and Medina, L. (2014). Combinatorial expression of Lef1, Lhx2, Lhx5, Lhx9, Lmo3, Lmo4, and Prox1 helps to identify comparable subdivisions in the developing hippocampal formation of mouse and chicken. *Front. Neuroanat.* 8:59. doi: 10.3389/fnana.2014.00059

Aboitiz, F., and Zamorano, F. (2013). Neural progenitors, patterning and ecology in neocortical origins. *Front. Neuroanat.* 7:38. doi: 10.3389/fnana.2013.00038

Achim, K., and Arendt, D. (2014). Structural evolution of cell types by step-wise assembly of cellular modules. *Curr. Opin. Genet. Dev.* 27C, 102–108. doi: 10.1016/j.gde.2014.05.001

Allen, T. A., and Fortin, N. J. (2013). The evolution of episodic memory. *Proc. Natl. Acad. Sci. U.S.A.* 110(Suppl), 10379–10386. doi: 10.1073/pnas.1301199110

Angevine, J. B., and Sidman, R. L. (1961). Autoradiographic study of cell migration during histogenesis of cerebral cortex in the mouse. *Nature* 192, 766–768. doi: 10.1038/192766b0

Arendt, D. (2008). The evolution of cell types in animals: emerging principles from molecular studies. *Nat. Rev. Genet.* 9, 868–882. doi: 10.1038/nrg2416

Ashwell, K. W., Marotte, L. R., Li, L., and Waite, P. M. (1996). Anterior commissure of the wallaby (*Macropus eugenii*): adult morphology and development. *J. Comp. Neurol.* 366, 478–494.

Atoji, Y., Wild, J. M., Yamamoto, Y., and Suzuki, Y. (2002). Intratelencephalic connections of the hippocampus in pigeons (*Columba livia*). *J. Comp. Neurol.* 447, 177–199. doi: 10.1002/cne.10239

Balthazart, J., and Ball, G. F. (2014). Doublecortin is a highly valuable endogenous marker of adult neurogenesis in canaries. Commentary on Vellema M et al. (2014): evaluating the predictive value of doublecortin as a marker for adult neurogenesis in canaries (*Serinus canaria*). *J. Comp. Brain Behav. Evol.* 84, 1–4. doi: 10.1159/000362917

Bayer, S. A. (1986). Neurogenesis in the rat primary olfactory cortex. *Int. J. Dev. Neurosci.* 4, 251–271. doi: 10.1016/0736-5748(86)90063-8

Belgard, T. G., Montiel, J. F., Wang, W. Z., García-Moreno, F., Margulies, E. H., Ponting, C. P., et al. (2013). Adult pallium transcriptomes surprise in not reflecting predicted homologies across diverse chicken and mouse pallial sectors. *Proc. Natl. Acad. Sci. U.S.A.* 110, 13150–13155. doi: 10.1073/pnas.1307444110

Brand, A. H., and Livesey, F. J. (2011). Neural stem cell biology in vertebrates and invertebrates: more alike than different? *Neuron* 70, 719–729. doi: 10.1016/j.neuron.2011.05.016

Brown, J. P., Couillard-Després, S., Cooper-Kuhn, C. M., Winkler, J., Aigner, L., and Kuhn, H. G. (2003). Transient expression of doublecortin during adult neurogenesis. *J. Comp. Neurol.* 467, 1–10. doi: 10.1002/cne.10874

Brox, A., Puelles, L., Ferreiro, B., and Medina, L. (2004). Expression of the genes Emx1, Tbr1, and Eomes (Tbr2) in the telencephalon of *Xenopus laevis* confirms the existence of a ventral pallial division in all tetrapods. *J. Comp. Neurol.* 474, 562–577. doi: 10.1002/cne.20152

Bruce, L. L. (2007). *Evolution of Nervous Systems*. Elsevier. doi: 10.1016/B0-12-370878-8/00130-0

Bruce, L. L., and Butler, A. B. (1984). Telencephalic connections in lizards. I. Projections to cortex. *J. Comp. Neurol.* 229, 585–601. doi: 10.1002/cne.902290411

Bruce, L. L., and Neary, T. J. (1995). The limbic system of tetrapods: a comparative analysis of cortical and amygdalar populations. *Brain Behav. Evol.* 46, 224–34. doi: 10.1159/000113276

Burwell, R. D., and Amaral, D. G. (1998a). Cortical afferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. *J. Comp. Neurol.* 398, 179–205.

Burwell, R. D., and Amaral, D. G. (1998b). Perirhinal and postrhinal cortices of the rat: interconnectivity and connections with the entorhinal cortex. *J. Comp. Neurol.* 391, 293–321.

Butler, A. B. (1976). Telencephalon of the lizard *Gekko gecko* (Linnaeus): some connections of the cortex and dorsal ventricular ridge. *Brain Behav. Evol.* 13, 396–417. doi: 10.1159/000123824

Butler, A. B. (1994). The evolution of the dorsal pallium in the telencephalon of amniotes: cladistic analysis and a new hypothesis. *Brain Res. Brain Res. Rev.* 19, 66–101. doi: 10.1016/0165-0173(94)90004-3

Butler, A. B., and Molnár, Z. (2002). Development and evolution of the collopallium in amniotes: a new hypothesis of field homology. *Brain Res. Bull.* 57, 475–479. doi: 10.1002/cne.1195

Butler, A. B., Reiner, A., and Karten, H. J. (2011). Evolution of the amniote pallium and the origins of mammalian neocortex. *Ann. N. Y. Acad. Sci.* 1225, 14–27. doi: 10.1111/j.1749-6632.2011.06006.x

Cai, Y., Xiong, K., Chu, Y., Luo, D.-W., Luo, X.-G., Yuan, X.-Y., Struble, R. G., et al. (2009). Doublecortin expression in adult cat and primate cerebral cortex relates to immature neurons that develop into GABAergic subgroups. *Exp. Neurol.* 216, 342–356. doi: 10.1016/j.expneurol.2008.12.008

Chen, C.-C., Winkler, C. M., Pfenning, A. R., and Jarvis, E. D. (2013). Molecular profiling of the developing avian telencephalon: regional timing and brain subdivision continuities. *J. Comp. Neurol.* 521, 3666–3701. doi: 10.1002/cne.23406

Cheung, A. F. P., Kondo, S., Abdel-Mannan, O., Chodroff, R. A., Sirey, T. M., Bluy, L. E., et al. (2010). The subventricular zone is the developmental milestone of a 6-layered neocortex: comparisons in metatherian and eutherian mammals. *Cereb. Cortex* 20, 1071–1081. doi: 10.1093/cercor/bhp168

Cheung, A. F. P., Pollen, A. A., Tavare, A., DeProto, J., and Molnár, Z. (2007). Comparative aspects of cortical neurogenesis in vertebrates. *J. Anat.* 211, 164–176. doi: 10.1111/j.1469-7580.2007.00769.x

Cobos, I., Puelles, L., and Martínez, S. (2001). The avian telencephalic subpallium originates inhibitory neurons that invade tangentially the pallium (dorsal ventricular ridge and cortical areas). *Dev. Biol.* 239, 30–45. doi: 10.1006/dbio.2001.0422

Couillard-Despres, S., Winner, B., Schaubeck, S., Aigner, R., Vroemen, M., Weidner, N., et al. (2005). Doublecortin expression levels in adult brain reflect neurogenesis. *Eur. J. Neurosci.* 21, 1–14. doi: 10.1111/j.1460-9568.2004.03813.x

De Lange, S. J. (1911). DasVorderhirn der Reptilien. *Folia Neuro-Biol Leitzig* 5, 548–597. doi: 10.1002/cne.1195

De Nevi, E., Marco-Salazar, P., Fondevila, D., Blasco, E., Pérez, L., and Pumarola, M. (2013). Immunohistochemical study of doublecortin and nucleostemin in canine brain. *Eur. J. Histochem.* 57:e9. doi: 10.4081/ejh.2013.e9

Desan. (1984). *The Organization of the Cerebral Cortex of the Pond Turtle, Pseudemys Scripta Elegans*. Ph.D. thesis. Available online at: http://www.its.caltech.edu/∼bi250b/2009/papers/Desan_1984.pdf

Desfilis, E., Font, E., Belekhova, M., and Kenigfest, N. (2002). Afferent and efferent projections of the dorsal anterior thalamic nuclei in the lizard *Podarcis hispanica* (Sauria, Lacertidae). *Brain Res. Bull.* 57, 447–450. doi: 10.1016/S0361-9230(01)00727-4

Dugas-Ford, J., Rowell, J. J., Ragsdale, C. W. (2012). Cell-type homologies and the origins of the neocortex. *Proc. Natl. Acad. Sci. U.S.A.* 109, 16974–16979. doi: 10.1073/pnas.1204773109

Ebner, F. F. (1976). "The forebrain of reptiles and mammals," in *Evolution of Brain and Behavior in Vertebrates*, eds R. B. Masterton, M. E. Bitterman, C. B. G. Campbell, and N. Hotton (Englewood Cliffs, NJ: Lawrence Erlbaum), 115–167.

Englund, C., Fink, A., Lau, C., Pham, D., Daza, R. A., Bulfone, A., et al. (2005). Pax6, Tbr2, and Tbr1 are expressed sequentially by radial glia, intermediate progenitor cells, and postmitotic neurons in developing neocortex. *J. Neurosci.* 25, 247–251. doi: 10.1523/JNEUROSCI.2899-04.2005

Eroglu, E., Burkard, T. R., Jiang, Y., Saini, N., Homem, C. C. F., Reichert, H., et al. (2014). SWI/SNF complex prevents lineage reversion and induces temporal patterning in neural stem cells. *Cell* 156, 1259–73. doi: 10.1016/j.cell.2014.01.053

Felleman, D. J., and Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cortex* 1, 1–47. doi: 10.1002/cne.1195

Fernandez, A. S., Pieau, C., Repérant, J., Boncinelli, E., and Wassef, M. (1998). Expression of the Emx-1 and Dlx-1 homeobox genes define three molecularly distinct domains in the telencephalon of mouse, chick, turtle and frog embryos: implications for the evolution of telencephalic subdivisions in amniotes. *Development* 125, 2099–111.

Fournier, J., Müller, C. M., Laurent, G. (2015). Looking for the roots of cortical sensory computation in three-layered cortices. *Curr. Opin. Neurobiol.* 31, 119–126. doi: 10.1016/j.conb.2014.09.006

Francis, F., Koulakoff, A., Boucher, D., Chafey, P., Schaar, B., Vinet, M. C., et al. (1999). Doublecortin is a developmentally regulated, microtubule-associated protein expressed in migrating and differentiating neurons. *Neuron* 23, 247–256. doi: 10.1016/S0896-6273(00)80777-1

Friocourt, G. (2003). Doublecortin functions at the extremities of growing neuronal processes. *Cereb. Cortex* 13, 620–626. doi: 10.1093/cercor/13.6.620

Fung, S. J., Joshi, D., Allen, K. M., Sivagnanasundaram, S., Rothmond, D. A., Saunders, R., et al. (2011). Developmental patterns of doublecortin expression and white matter neuron density in the postnatal primate prefrontal cortex and schizophrenia. *PLoS ONE* 6:e25194. doi: 10.1371/journal.pone.0025194

Gao, P., Postiglione, M. P., Krieger, T. G., Hernandez, L., Wang, C., Han, Z., et al. (2014). Deterministic progenitor behavior and unitary production of neurons in the neocortex. *Cell* 159, 775–788. doi: 10.1016/j.cell.2014.10.027

Gatome, C. W., Mwangi, D. K., Lipp, H.-P., and Amrein, I. (2010). Hippocampal neurogenesis and cortical cellular plasticity in Wahlberg's epauletted fruit bat: a qualitative and quantitative study. *Brain Behav. Evol.* 76, 116–127. doi: 10.1159/000320210

Gilbert, C. D., and Sigman, M. (2007). Brain states: top-down influences in sensory processing. *Neuron* 54, 677–96. doi: 10.1016/j.neuron.2007.05.019

Gleeson, J. G., Lin, P. T., Flanagan, L. A., and Walsh, C. A. (1999). Doublecortin is a microtubule-associated protein and is expressed widely by migrating neurons. *Neuron* 23, 257–71. doi: 10.1016/S0896-6273(00)80778-3

Goffinet, A. M., Daumerie, C., Langerwerf, B., Pieau, C. (1986). Neurogenesis in reptilian cortical structures: 3H-thymidine autoradiographic analysis. *J. Comp. Neurol.* 243, 106–116. doi: 10.1002/cne.902430109

Gómez-Climent, M. A., Castillo-Gómez, E., Varea, E., Guirado, R., Blasco-Ibáñez, J. M., Crespo, C., et al. (2008). A population of prenatally generated cells in the rat paleocortex maintains an immature neuronal phenotype into adulthood. *Cereb. Cortex* 18, 2229–2240. doi: 10.1093/cercor/bhm255

Greig, L. C., Woodworth, M. B., Galazo, M. J., Padmanabhan, H., and Macklis, J. D. (2013). Molecular logic of neocortical projection neuron specification, development and diversity. *Nat. Rev. Neurosci.* 14, 755–769. doi: 10.1038/nrn3586

Guirado, S., and Dávila, J. C. (2002). Thalamo-telencephalic connections: new insights on the cortical organization in reptiles. *Brain Res. Bull.* 57, 451–454. doi: 10.1016/S0361-9230(01)00677-3

Haberly, L. B. (1990). "Comparative aspects of olfactory cortex," in *Cerebral Cortex. Vol 8B: Comparative Structure and Evolution of Cerebral Cortex*, eds E. G. Jones and A. Peters (New York, NY: Plenum), 137–166. doi: 10.1007/978-1-4615-3824-0_2

Haberly, L. B. (2001). Parallel-distributed processing in olfactory cortex: new insights from morphological and physiological analysis of neuronal circuitry. *Chem. Senses* 26, 551–576. doi: 10.1093/chemse/26.5.551

Hall, B. K., and Gillis, J. A. (2013). Incremental evolution of the neural crest, neural crest cells and neural crest-derived skeletal tissues. *J. Anat.* 222, 19–31. doi: 10.1111/j.1469-7580.2012.01495.x

Hevner, R. F., Hodge, R. D., Daza, R. A., Englund, C. (2006). Transcription factors in glutamatergic neurogenesis: conserved programs in neocortex, cerebellum, and adult hippocampus. *Neurosci. Res.* 55, 223–233. doi: 10.1016/j.neures.2006.03.004

Hoogland, P. V., and Vermeulen-Vanderzee, E. (1989). Efferent connections of the dorsal cortex of the lizard Gekko gecko studied with Phaseolus vulgaris-leucoagglutinin. *J. Comp. Neurol.* 285, 289–303. doi: 10.1002/cne.902850302

Hoogland, P. V., and Vermeulen-Vanderzee, E. (1995). Efferent connections of the lateral cortex of the lizard Gekko gecko: evidence for separate origins of medial and lateral pathways from the lateral cortex to the hypothalamus. *J. Comp. Neurol.* 352, 469–80. doi: 10.1002/cne.903520311

Ishizuka, N. (2001). Laminar organization of the pyramidal cell layer of the subiculum in the rat. *J. Comp. Neurol.* 435, 89–110 doi: 10.1002/cne.1195

Jones, B. F., and Witter, M. P. (2007). Cingulate cortex projections to the parahippocampal region and hippocampal formation in the rat. *Hippocampus* 17, 957–76. doi: 10.1002/hipo.20330

Jones, E. G. (1975). Varieties and distribution of non-pyramidal cells in the somatic sensory cortex of the squirrel monkey. *J. Comp. Neurol.* 160, 205–67. doi: 10.1002/cne.901600204

Kappers, A. C. U. (1909). The phylogenesis of the paleocortex and archicortex compared with the evolution of the visual neocortex. *Arch. Neurol.* 4, 161–272.

Kappers, A. C. U., and Theunissen, W. F., (1908). Die Phylogenese des Rhinencephalon des Corpus striatum und derVorderhirnkommissuren. *Folia Neurobiol.* 1, 173–288. doi: 10.1002/cne.1195

Karten, H. J. (1969). The organization of the avian telencephalon and some speculations on the phylogeny of the amniote telencephalon. *Ann. N. Y. Acad. Sci.* 167, 164–179. doi: 10.1111/j.1749-6632.1969.tb20442.x

Karten, H. J. (2013). Neocortical evolution: neuronal circuits arise independently of lamination. *Curr. Biol.* 23, R12–R15. doi: 10.1016/j.cub.2012.11.013

Klempin, F., Kronenberg, G., Cheung, G., Kettenmann, H., and Kempermann, G. (2011). Properties of doublecortin-(DCX)-expressing cells in the piriform cortex compared to the neurogenic dentate gyrus of adult mice. *PLoS ONE* 6:e25760. doi: 10.1371/journal.pone.0025760

Knierim, J. J., Neunuebel, J. P., and Deshmukh, S. S. (2014). Functional correlates of the lateral and medial entorhinal cortex: objects, path integration and local-global reference frames. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 369:20130369. doi: 10.1098/rstb.2013.0369

Kowalczyk, T., Pontious, A., Englund, C., Daza, R. A. M., Bedogni, F., Hodge, R., et al. (2009). Intermediate neuronal progenitors (basal progenitors) produce pyramidal-projection neurons for all layers of cerebral cortex. *Cereb. Cortex* 19, 2439–50. doi: 10.1093/cercor/bhn260

Lein, E. S., Hawrylycz, M. J., Ao, N., Ayres, M., Bensinger, A., Bernard, A., et al. (2007). Genome-wide atlas of gene expression in the adult mouse brain. *Nature* 445, 168–176. doi: 10.1038/nature05453

Lewitus, E., Kelava, I., Kalinka, A. T., Tomancak, P., and Huttner, W. B. (2014). An adaptive threshold in mammalian neocortical evolution. *PLoS Biol.* 12:e1002000. doi: 10.1371/journal.pbio.1002000

Li, X., Chen, Z., and Desplan, C. (2013a). Temporal patterning of neural progenitors in Drosophila. *Curr. Top. Dev. Biol.* 105, 69–96. doi: 10.1016/B978-0-12-396968-2.00003-8

Li, X., Erclik, T., Bertet, C., Chen, Z., Voutev, R., Venkatesh, S., et al. (2013b). Temporal patterning of Drosophila medulla neuroblasts controls neural fates. *Nature* 498, 456–462. doi: 10.1038/nature12319

Luzzati, F., Bonfanti, L., Fasolo, A., and Peretto, P. (2009). DCX and PSA-NCAM expression identifies a population of neurons preferentially distributed in associative areas of different pallial derivatives and vertebrate species. *Cereb. Cortex* 19, 1028–1041. doi: 10.1093/cercor/bhn145

Luzzati, F., De Marchis, S., Fasolo, A., and Peretto, P. (2006). Neurogenesis in the caudate nucleus of the adult rabbit. *J. Neurosci.* 26, 609–621. doi: 10.1523/JNEUROSCI.4371-05.2006

Martínez-Cerdeño, V., Noctor, S. C., and Kriegstein, A. R. (2006). The role of intermediate progenitor cells in the evolutionary expansion of the cerebral cortex. *Cereb. Cortex* 16(Suppl. 1), i152–i161. doi: 10.1093/cercor/bhk017

Martinez-Garcia, F., Olucha, F. E., Teruel, V., Lorente, M. J., and Schwerdtfeger, W. K. (1991). Afferent and efferent connections of the olfactory bulbs in the lizard *Podarcis hispanica*. *J. Comp. Neurol.* 305, 337–47. doi: 10.1002/cne.903050214

Martinez-Garcia, F., Amiguet, M., Schwerdtfeger, W. K., Olucha, F. E., and Lorente, M. J. (1990). Interhemispheric connections through the pallial commissures in the brain of *Podarcis hispanica* and *Gallotia stehlinii* (Reptilia, Lacertidae). *J. Morphol.* 205, 17–31. doi: 10.1002/jmor.1052050104

Medina, L., Abellán, A., and Desfilis, E. (2013). A never-ending search for the evolutionary origin of the neocortex: rethinking the homology concept. *Brain Behav. Evol.* 81, 150–153. doi: 10.1159/000348282

Meulemans, D., and Bronner-Fraser, M. (2007). Insights from amphioxus into the evolution of vertebrate cartilage. *PLoS ONE* 2:e787. doi: 10.1371/journal.pone.0000787

Minelli, G. (1967). Considerazioni anatomo-com par"tive sulle corteccie dei Rettili. *Arch. Zool. Ital.* 52, 75–88.

Montiel, J. F., and Molnár, Z. (2013). The impact of gene expression analysis on evolving views of avian brain organization. *J. Comp. Neurol.* 521, 3604–3613. doi: 10.1002/cne.23403

Nacher, J., Crespo, C., and McEwen, B. S. (2001). Doublecortin expression in the adult rat telencephalon. *Eur. J. Neurosci.* 14, 629–644. doi: 10.1046/j.0953-816x.2001.01683.x

Nielsen, J. V., Nielsen, F. H., Ismail, R., Noraberg, J., and Jensen, N. A. (2007). Hippocampus-like corticoneurogenesis induced by two isoforms of the BTB-zinc finger gene Zbtb20 in mice. *Development* 134, 1133–1140. doi: 10.1242/dev.000265

Nielsen, J. V., Thomassen, M., Møllgård, K., Noraberg, J., and Jensen, N. A. (2014). Zbtb20 defines a hippocampal neuronal identity through direct repression of genes that control projection neuron development in the isocortex. *Cereb. Cortex* 24, 1216–29. doi: 10.1093/cercor/bhs400

Nieuwenhuys, R. (1994). The neocortex: an overview of its evolutionary development, structural organization and synaptology. *Anat. Embryol. (Berl)* 190, 307–337. doi: 10.1007/BF00187291

Nomura, T., Gotoh, H., and Ono, K. (2013). Changes in the regulation of cortical neurogenesis contribute to encephalization during amniote brain evolution. *Nat. Commun.* 4, 2206. doi: 10.1038/ncomms3206

Nomura, T., Murakami, Y., Gotoh, H., and Ono, K. (2014). Reconstruction of ancestral brains: exploring the evolutionary process of encephalization in amniotes. *Neurosci. Res.* 86C, 25–36. doi: 10.1016/j.neures.2014.03.004

Nomura, T., Takahashi, M., Hara, Y., and Osumi, N. (2008). Patterns of neurogenesis and amplitude of Reelin expression are essential for making a mammalian-type cortex. *PLoS ONE* 3:e1454. doi: 10.1371/journal.pone.0001454

Olude, A. M., Olopade, J. O., and Ihunwo, A. O. (2014). Adult neurogenesis in the African giant rat (Cricetomysgambianus, waterhouse). *Metab. Brain Dis.* 29, 857–66. doi: 10.1007/s11011-014-9512-9

Puelles, L. (2001). Thoughts on the development, structure and evolution of the mammalian and avian telencephalic pallium. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1583–1598. doi: 10.1098/rstb.2001.0973

Puelles, L. (2011). Pallio-pallial tangential migrations and growth signaling: new scenario for cortical evolution? *Brain Behav. Evol.* 78, 108–127. doi: 10.1159/000327905

Puelles, L., Kuwana, E., Puelles, E., Bulfone, A., Shimamura, K., Keleher, J., et al. (2000). Pallial and subpallial derivatives in the embryonic chick and mouse telencephalon, traced by the expression of the genes Dlx-2, Emx-1, Nkx-2.1, Pax-6, and Tbr-1. *J. Comp. Neurol.* 424, 409–438. doi: 10.1002/1096-9861(20000828)424:3<409::AID-CNE3>3.0.CO;2-7

Rakic, P. (1995). A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. *Trends Neurosci.* 18, 383–388. doi: 10.1016/0166-2236(95)93934-P

Rattenborg, N. C., and Martinez-Gonzalez, D. (2011). A bird-brain view of episodic memory. *Behav. Brain Res.* 222, 236–245. doi: 10.1016/j.bbr.2011.03.030

Regidor, G. (1977). *Tipología Neuronal y Organización de la Corteza Cerebral de Lacerta Galloti (Dum. y Bib.): Estudio Con los Métodos de GOLGI*. Available online at: http://mdc.ulpgc.es/cdm/singleitem/collection/MDC/id/1326/rec/1

Reiner, A. (1991). A comparison of neurotransmitter-specific and neuropeptide-specific neuronal cell types present in the dorsal cortex in turtles with those present in the isocortex in mammals: implications for the evolution of isocortex. *Brain. Behav. Evol.* 38, 53–91. doi: 10.1159/000114379

Reiner, A. (1993). Neurotransmitter organization and connections of turtle cortex: implications for the evolution of mammalian isocortex. *Comp. Biochem. Physiol. Comp. Physiol.* 104, 735–748. doi: 10.1016/0300-9629(93)90149-X

Reiner, A. J. (2000). A hypothesis as to the organization of cerebral cortex in the common amniote ancestor of modern reptiles and mammals. *Novartis Found. Symp.* 228, 83–102. discussion: 102–113. doi: 10.1002/0470846631.ch7

Rosenthal, E. H., Tonchev, A. B., Stoykova, A., and Chowdhury, K. (2012). Regulation of archicortical arealization by the transcription factor Zbtb20. *Hippocampus* 22, 2144–2156. doi: 10.1002/hipo.22035

Rouaux, C., and Arlotta, P. (2013). Direct lineage reprogramming of post-mitotic callosal neurons into corticofugal neurons *in vivo*. *Nat. Cell Biol.* 15, 214–221. doi: 10.1038/ncb2660

Rowe, T. B., Macrini, T. E., and Luo, Z.-X. (2011). Fossil evidence on origin of the mammalian brain. *Science* 332, 955–957. doi: 10.1126/science.1203117

Sanides, F. (1969). Comparative architectonics of the neocortex of mammals and their evolutionary interpretation. *Ann. N. Y. Acad. Sci.* 167, 404–423. doi: 10.1111/j.1749-6632.1969.tb20459.x

Sanides, F., and Sanides, D. (1972). The "extraverted neurons" of the mammalian cerebral cortex. *Z. Anat. Entwicklungsgesch.* 136, 272–293. doi: 10.1007/BF00522616

Sassoè-Pognetto, M., Artero, C., Mazzi, V., and Franzoni, M. F. (1995). Connections of the posterior pallium in the crested newt, *Triturus carnifex*. *Brain Behav. Evol.* 45, 195–208. doi: 10.1159/000113550

Schepers, G. W. H. (1948). *Evolution of the Forebrain*. Cape Town, Maskew Miller.

Shepherd, G. M. (2011). The microcircuit concept applied to cortical evolution: from three-layer to six-layer cortex. *Front. Neuroanat.* 5:30. doi: 10.3389/fnana.2011.00030

Shipley, M. T., and Geinisman, Y. (1984). Anatomical evidence for convergence of olfactory, gustatory, and visceral afferent pathways in mouse cerebral cortex. *Brain Res. Bull.* 12, 221–226. doi: 10.1016/0361-9230(84)90049-2

Shubin, N., Tabin, C., Carroll, S. (2009). Deep homol- ogy and the origins of evolutionary novelty. *Nature* 457, 818–823. doi: 10.1038/nature07891

Striedter, G. F. (1997). The telencephalon of tetrapods in evolution. *Brain. Behav. Evol.* 49, 179–213. doi: 10.1159/000112991

Suárez, R., Gobius, I., and Richards, L. J. (2014). Evolution and development of interhemispheric connections in the vertebrate forebrain. *Front. Hum. Neurosci.* 8:497. doi: 10.3389/fnhum.2014.00497

Sutton, E., Hughes, J., White, S., Sekido, R., Tan, J., Arboleda, V., et al. (2011). Identification of SOX3 as an XX male sex reversal gene in mice and humans. *J. Clin. Invest.* 121, 328–341. doi: 10.1172/JCI42580

Suzuki, I. K., and Hirata, T. (2013). Neocortical neurogenesis is not really "neo": a new evolutionary model derived from a comparative study of chick pallial development. *Dev. Growth Differ.* 55, 173–187. doi: 10.1111/dgd.12020

Suzuki, I. K., and Hirata, T. (2014). A common developmental plan for neocortical gene-expressing neurons in the pallium of the domestic chicken *Gallus gallus domesticus* and the Chinese softshell turtle *Pelodiscus sinensis*. *Front. Neuroanat.* 8:20. doi: 10.3389/fnana.2014.00020

Suzuki, I. K., Kawasaki, T., Gojobori, T., and Hirata, T. (2012). The temporal sequence of the mammalian neocortical neurogenetic program drives mediolateral pattern in the chick pallium. *Dev. Cell* 22, 863–870. doi: 10.1016/j.devcel.2012.01.004

Takehana, Y., Matsuda, M., Myosho, T., Suster, M. L., Kawakami, K., Shin,-I. T., et al. (2014). Co-option of Sox3 as the male-determining factor on the Y chromosome in the fish Oryzias dancena. *Nat. Commun.* 5, 4157. doi: 10.1038/ncomms5157

Tarabykin, V., Stoykova, A., Usman, N., and Gruss, P. (2001). Cortical upper layer neurons derive from the subventricular zone as indicated by Svet1 gene expression. *Development* 128, 1983–1993.

Teissier, A., Griveau, A., Vigier, L., Piolot, T., Borello, U., and Pierani, A. (2010). A novel transient glutamatergic population migrating from the pallial-subpallial boundary contributes to neocortical development. *J. Neurosci.* 30, 10563–10574. doi: 10.1523/JNEUROSCI.0776-10.2010

Teissier, A., Waclaw, R. R., Griveau, A., Campbell, K., and Pierani, A. (2012). Tangentially migrating transient glutamatergic neurons control neurogenesis and maintenance of cerebral cortical progenitor pools. *Cereb. Cortex* 22, 403–416. doi: 10.1093/cercor/bhr122

True, J. R., and Carroll, S. B. (2002). Gene co-option in physiological and morphological evolution. *Annu. Rev. Cell Dev. Biol.* 18, 53–80. doi: 10.1146/annurev.cellbio.18.020402.140619

Ulinsky, P. S. (1990). "The cerebral cortex of reptiles," in *Cerebral Cortex. Vol 8A: Comparative Structure and Evolution of Cerebral Cortex*, eds E. G. Jones and A. Peters (New York, NY: Plenum), 139–215. doi: 10.1007/978-1-4757-9622-3_5

Wichterle, H., Turnbull, D. H., Nery, S., Fishell, G., and Alvarez-Buylla, A. (2001). *In utero* fate mapping reveals distinct migratory pathways and fates of neurons born in the mammalian basal forebrain. *Development* 128, 3759–3771.

Wilson, D. A., and Sullivan, R. M. (2011). Cortical processing of odor objects. *Neuron* 72, 506–519. doi: 10.1016/j.neuron.2011.10.027

Xiong, K., Luo, D.-W., Patrylo, P. R., Luo, X.-G., Struble, R. G., Clough, R. W., et al. (2008). Doublecortin-expressing cells are present in layer II across the adult guinea pig cerebral cortex: partial colocalization with mature interneuron markers. *Exp. Neurol.* 211, 271–282. doi: 10.1016/j.expneurol.2008.02.003

Zeier, H. J., and Karten, H. J. (1973). Connections of the anterior commissure in the pigeon (*Columba livia*). *J. Comp. Neurol.* 150, 201–216. doi: 10.1002/cne.901500207

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neuroscience

ORIGINAL RESEARCH
published: 28 July 2015
doi: 10.3389/fnins.2015.00251

Ontogenetic shifts in brain scaling reflect behavioral changes in the life cycle of the pouched lamprey *Geotria australis*

Carlos A. Salas[1]*, *Kara E. Yopak*[1], *Rachael E. Warrington*[1], *Nathan S. Hart*[1], *Ian C. Potter*[2] and *Shaun P. Collin*[1]

[1] Neuroecology Group, School of Animal Biology and UWA Oceans Institute, The University of Western Australia, Crawley, WA, Australia, [2] Centre for Fish and Fisheries Research, School of Veterinary and Life Sciences, Murdoch University, Murdoch, WA, Australia

Very few studies have described brain scaling in vertebrates throughout ontogeny and none in lampreys, one of the two surviving groups of the early agnathan (jawless) stage in vertebrate evolution. The life cycle of anadromous parasitic lampreys comprises two divergent trophic phases, firstly filter-feeding as larvae in freshwater and secondly parasitism as adults in the sea, with the transition marked by a radical metamorphosis. We characterized the growth of the brain during the life cycle of the pouched lamprey *Geotria australis*, an anadromous parasitic lamprey, focusing on the scaling between brain and body during ontogeny and testing the hypothesis that the vast transitions in behavior and environment are reflected in differences in the scaling and relative size of the major brain subdivisions throughout life. The body and brain mass and the volume of six brain structures of *G. australis*, representing six points of the life cycle, were recorded, ranging from the early larval stage to the final stage of spawning and death. Brain mass does not increase linearly with body mass during the ontogeny of *G. australis*. During metamorphosis, brain mass increases markedly, even though the body mass does not increase, reflecting an overall growth of the brain, with particularly large increases in the volume of the optic tectum and other visual areas of the brain and, to a lesser extent, the olfactory bulbs. These results are consistent with the conclusions that ammocoetes rely predominantly on non-visual and chemosensory signals, while adults rely on both visual and olfactory cues.

Keywords: growth, agnathan, lifestyle, filter feeder, heterochrony, jawless vertebrate, metamorphosis, parasite

OPEN ACCESS

Edited by:
Jorge Mpodozis, Universidad de Chile, Chile

Reviewed by:
Andrew Iwaniuk, University of Lethbridge, Canada
Thomas Lisney, University of Western Australia, Australia

***Correspondence:**
Carlos A. Salas, Neuroecology Group, School of Animal Biology, The University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia
carlos.salas.uwa@gmail.com

Specialty section:
This article was submitted to Evolutionary Psychology and Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *17 April 2015*
Accepted: *03 July 2015*
Published: *28 July 2015*

Citation:
Salas CA, Yopak KE, Warrington RE, Hart NS, Potter IC and Collin SP (2015) Ontogenetic shifts in brain scaling reflect behavioral changes in the life cycle of the pouched lamprey Geotria australis. Front. Neurosci. 9:251. doi: 10.3389/fnins.2015.00251

Introduction

Lampreys are extant relatives of an early and diverse group of jawless vertebrates (Kumar and Hedges, 1998; Heimberg et al., 2008; Janvier, 2008; Smith et al., 2013). The results of early studies on the agnathan nervous system (Johnston, 1902; Heier, 1948; Nieuwenhuys, 1977) have thus been used as an indicator of the ancestral condition of the vertebrate brain (Fritzsch and Northcutt, 1993a; Butler and Hodos, 1996; Northcutt, 2002; Gilland and Baker, 2005; Khonsari et al., 2009; Suárez et al., 2014). The design or bauplan of the vertebrate brain and the developmental mechanisms that underlie their subdivisions are considered to be highly conserved

(Striedter, 2005; Ota and Kuratani, 2007; Guerin et al., 2009; Charvet et al., 2011). However, it is expected that the various sensory modalities and other neural specializations will evolve, to a degree, in association with ecological niche, and that this relationship will be reflected in adapted behaviors and/or enhanced cognitive capabilities (Barton et al., 1995; Barton and Harvey, 2000; De Winter and Oxnard, 2001). Indeed, brain size and the relative development of major brain subdivisions vary at intraspecific, interspecific, and ontogenetic levels across a range of vertebrates (e.g., Kruska, 2005; Gonda et al., 2013) in relation to factors such as life style, habitat, and behavior (e.g., Pollen et al., 2007; Yopak and Montgomery, 2008; Barton and Capellini, 2011), as well as phylogenetic and developmental constraints (e.g., Finlay and Darlington, 1995; Yopak et al., 2010).

The size of the brain relative to the body (scaling) has long since been used in studies of brain development and evolution (Ariëns Kapper, 1936; Gould, 1975; Deacon, 1990; Aboitiz, 1996), in which brain mass (E) is characterized as a function of body mass (S) with Snell's formula: $E = k^{*}S^{\propto}$ or $\log E = \propto \log S + k$, where $\propto$= allometric slope or scaling power. It is a common assumption that encephalization (a larger than expected brain size for a given body size) reflects enhanced cognitive capabilities (Jerison, 1977; Ebbesson, 1980; Lefebvre et al., 2004), although this is still the subject of debate (Healy and Rowe, 2007; Herculano-Houzel, 2012). Previous studies have examined encephalization of the brain of jawless fishes (Platel and Delfini, 1981; Ebinger et al., 1983; Platel and Vesselkin, 1989; Wicht, 1996) and have shown that agnathans, particularly lampreys, possess a relatively small brain and some of the highest degrees of intraspecific variation in brain and body mass when compared to any other vertebrate group (Ebinger et al., 1983; Platel and Delfini, 1986). However, these data have been collected from very few species and no consideration has yet been given to changes in encephalization and brain organization that may occur throughout their life cycle. Indeed, ontogenetic studies of diverse groups of vertebrates have shown that the brain grows at different rates during their lifespan, with the rates being greatest in the embryonic and early postnatal phases (Bauchot et al., 1979; Gille and Salomon, 2000; Fu et al., 2013; Ngwenya et al., 2013). Although some studies have shown shifts in ecology and corresponding shifts in brain development occur in fishes (e.g., Brandstätter and Kotrschal, 1990; Wagner, 2003; Lisney et al., 2007; Iribarne and Castelló, 2014), there are no data on the pattern of encephalization or brain subdivision scaling during the ontogeny of lampreys.

The life cycle of lampreys is very conserved (Chang et al., 2014; Potter et al., 2015), consisting of a prolonged and sedentary larval phase, followed by metamorphosis into the free-swimming adult phase (Manzon et al., 2015), as illustrated in **Figure 1**. In the pouched lamprey *Geotria australis*, which is widely distributed in temperate regions of the southern hemisphere (Renaud, 2011), the life cycle has an approximate duration of 8 years (Potter et al., 1980, 1983; Potter and Hilliard, 1986).

After hatching, the larvae (ammocoetes) burrow in the soft sediments of streams and rivers, filtering detritus, algae and other organisms from the overlying water (Piavis, 1971; Moore and Mallat, 1980; Richardson et al., 2010; Dawson et al., 2015). Ammocoetes have rudimentary eyes with a largely undifferentiated retina (Meyer-Rochow and Stewart, 1996; Villar-Cheda et al., 2008), and also a well-developed non-visual photoreceptive system, e.g., the pineal organ (García-Fernández and Foster, 1994; Deliagina et al., 1995; Melendez-Ferro et al., 2002; Vigh et al., 2002). In fact, they exhibit nocturnal habits with synchronized, seasonal downstream movements (Gritzenko, 1968; Potter, 1980), which may be controlled by circadian rhythms. An octaval lateral line system provide additional mechano-, electro-, and photo-perception, with photoreception being mediated by dermal non-visual photoreceptors located in the tail (Ronan, 1988; Ronan and Bodznick, 1991; Deliagina et al., 1995; Gelman et al., 2007). Ammocoetes also have well-developed gustatory (Baatrup, 1985; Barreiro-Iglesias et al., 2010) and olfactory (Vandenbossche et al., 1995; Zielinski et al., 2005) systems, and behavioral evidence has revealed that rotting potato haulms attracted ammocoetes when placed on the bed of freshwater streams (Enequist, 1937; Hardisty and Potter, 1971), indicating that they may actively search for food using chemosensory cues. Therefore, taste and olfaction are likely important drivers of their behavior.

The metamorphosis of anadromous parasitic species of lampreys, such as *G. australis,* involves major morphological and physiological changes and the development of new sensory and motor capabilities. These include the development of image-forming eyes with the potential for pentachromacy in *G. australis* (Meyer-Rochow and Stewart, 1996; Collin et al., 1999, 2003; Davies et al., 2007), a reduction of lateral line-mediated negative phototaxis that marks a switch from non-visual to visual perception (Binder et al., 2013), the rearrangement of the gustatory and lateral line systems (Currie and Carlsen, 1988; Jørgensen, 2005; Gelman et al., 2008; Barreiro-Iglesias et al., 2010), and the development of a tooth-bearing suctorial disc and "tongue-like" piston with the associated musculature and trigeminal motor innervation (Homma, 1978; Lethbridge and Potter, 1981). Metamorphosis also involves fundamental changes in a number of internal organs, including the intestine and gills, which enable the lamprey to osmoregulate in the sea (Youson et al., 1977; Hilliard et al., 1983; Bartels and Potter, 2004; Reis-Santos et al., 2008).

During the marine parasitic phase, *G. australis* swims toward and attaches to a host, often a teleost fish, and feeds from its flesh (Hilliard et al., 1985; Renaud et al., 2009), thereby increasing in body size from approximately 100 mm and 0.75 g to 620 mm and 220 g (Potter et al., 1980, 1983). There is strong evidence that during its marine parasitic phase, *G. australis* occupies an epipelagic niche in the sea and exhibits diurnal habits (Potter et al., 1979; Cobley, 1996; Collin et al., 1999; Davies et al., 2007). Following the completion of the parasitic phase, the adult lamprey re-enters rivers cued mainly by pheromones that are released by the ammocoetes (Vrieze and Sorensen, 2001; Sorensen et al., 2005; Vrieze et al., 2010, 2011), where they migrate upstream at night (Jellyman et al., 2002; Binder and McDonald, 2007; Vrieze et al., 2011). *Geotria australis* does not feed during its exceptionally long spawning run, using body reserves accumulated during the marine phase to develop secondary sexual characters and mature gonads (Potter et al., 1983; Paton et al., 2011). The life cycle culminates in spawning and subsequent death.

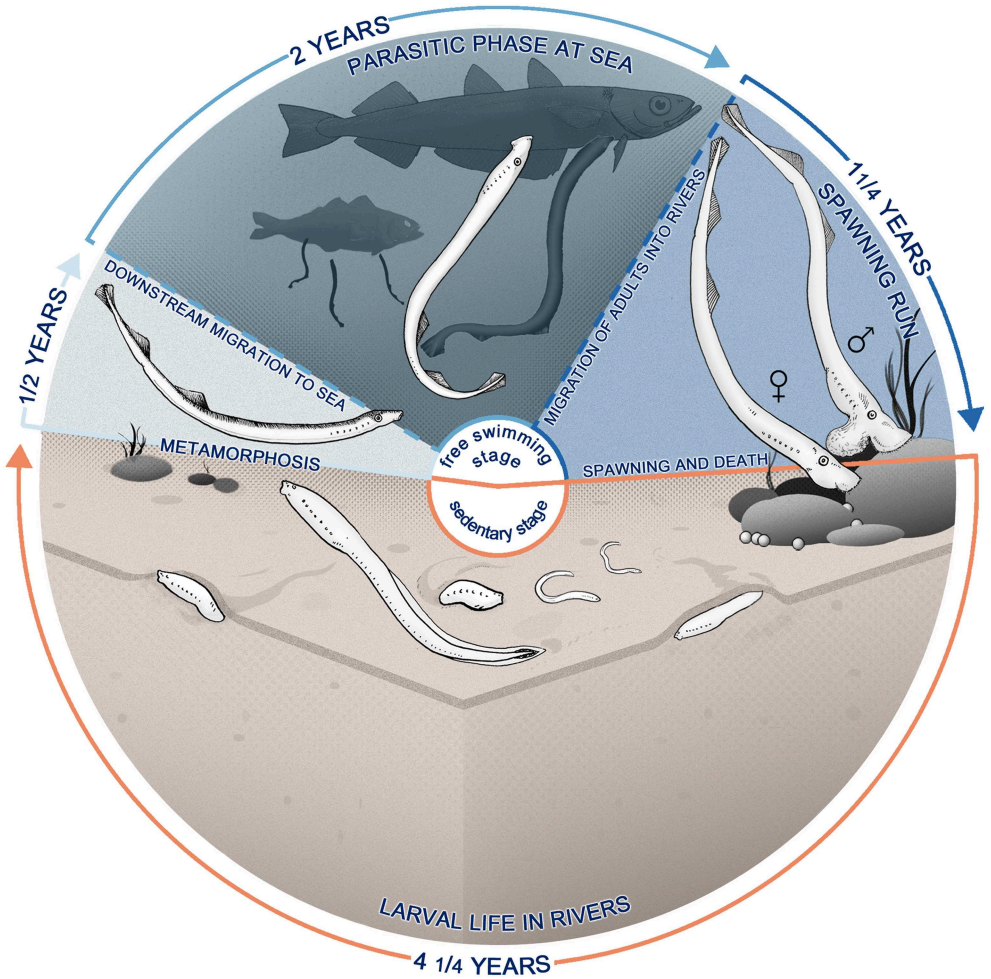


FIGURE 1 | Life cycle of *Geotria australis* presenting anadromous reproductive and feeding migrations. After hatching (**bottom**), the larvae—also called ammocoetes—burrow in the sediments of rivers, becoming a microphagous filter-feeder for approximately 4 years. The larval phase is followed by a metamorphosis, a non-feeding transition to adult stage that lasts for approximately 6 months (**left**), where there is a marked transformation in most of the body systems. Animals at this stage start migrating downstream and enter the sea, where they locate a teleost host and feed on its flesh using a specialized buccal apparatus (**top**). *G. australis* return years later to the rivers, where they start a long upstream migration, subsisting only on body reserves, which are expended in developing secondary sexual characteristics and reproductive behavior. Upstream migrants finally spawn and die (**right**).

During its life cycle, *G. australis* occupies different ecological niches and encounters diverse environmental conditions, yet there have been no comprehensive studies that have quantified the changes in brain organization corresponding to these marked changes in ecology and behavior. In this study, we assess changes in relative brain size (encephalization) and in the volume of six major brain structures (brain organization) at different phases of the life cycle in *G. australis*. We hypothesize that differences in brain size and organization will reflect the pronounced environmental and physiological changes that lampreys experience during ontogeny.

Methods

All the procedures described below were performed in accordance with the ethical guidelines of The University of Western Australia Animal Ethics Committee—Research Project RA/3/100/917.

Data Collection

Forty specimens of *G. australis* were analyzed in this study, representing six different points in their life cycle (ammocoetes of second, third, and fourth age class, downstream migrants, upstream migrants, and maturing adults). Specimens within a stage had the same fixation and preservation methods, as shown in Supplementary Table 1, and were captured in the same year (ammocoetes and downstream migrants) or in different years (upstream migrants and maturing adults). Morphometrics (body mass, body length, sex) were collected for each individual when possible. After a period of fixation, the brain was removed from the chondrocranium. The meninges were removed and the cranial nerves were cut to within 0.5 mm of the base. The brains were blotted and weighed to the nearest 0.1 mg (ammocoetes

and downstream migrants) or 1 mg (upstream migrants and maturing adults). Neither brain nor body mass were corrected for shrinkage due to fixation.

Photographs of the lateral and dorsal views of each brain were taken using a Leica EC3 camera attached to a Nikon SMZ-745T dissecting microscope. Brains were submerged in a solution of 0.1 M phosphate buffer while photographed to prevent volume distortions caused by dehydration of the tissue. Measurements of length were taken for each of the six brain structures as shown in **Figure 2**. Brain structures were determined from previously published descriptions of the brain and the cranial nerve distribution in lampreys (Nieuwenhuys and Nicholson, 1998). The length (l), height (h), and width (w) of the olfactory bulbs (OB), telencephalic hemispheres (Te), the pineal organ (PO), the optic tectum (OT), the octaval-trigeminal area (OCT; defined as the anterior region of the rhombencephalon comprising the V–VIII nerves), and the gustatory area (GUS; defined as the posterior region of the rhombencephalon comprising the IX–XII nerves) were measured using ImageJ (Rasband, 1997) as described previously (Huber et al., 1997; Wagner, 2001; Yopak and Lisney, 2012). The pineal organ was dissected out of the brain and photographed separately, see **Figure 2B**.

Volumes of each major brain structure were estimated using the ellipsoid method, which approximates the volume of a structure by assuming it takes the shape of an idealized ellipsoid, or a fraction of it as shown below (Huber et al., 1997; Wagner, 2001). The general formula of an ellipsoid is:

$$V = \frac{4}{3}\pi\, a\, b\, c$$

where *a, b, c* are the radii of the ellipsoid. Using the measurements of length (*l*), height (*h*), and width (*w*) shown for each structure in **Figure 2**, the volumes were defined as:

$$V = \frac{1}{6}\pi\, l\, h\, w$$

for the OB, Te, PO, and the OT, which were all modeled as half ellipsoids,

$$V = \frac{1}{3}\pi\, l\, h\, w$$

while the volume of the OCT and GUS were modeled as a quarter of an ellipsoid. In the case of bilateral structures (i.e., OB, Te, and TO), the values of the volumes were doubled. Volume estimates were not corrected for ventricular volume. Total brain volume was calculated from total brain mass using the estimated density of the brain tissue, $d = 1.036\ \mathrm{mg/mm^3}$ (Stephan, 1960).

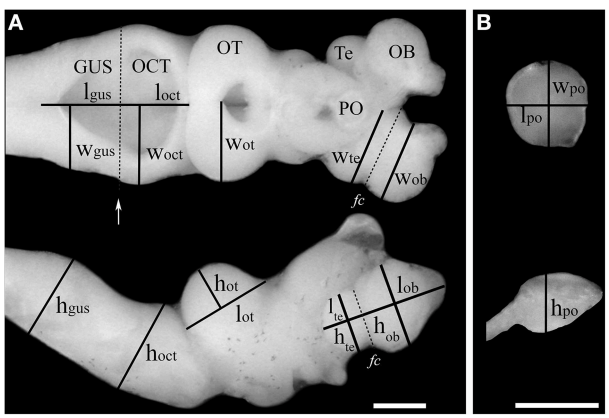


FIGURE 2 | Estimation of the volume of brain structures using the ellipsoid method. Measurements of length (l), width (w), and height (h) of six brain structures taken from a dorsal view **(A,** top) or lateral view **(A,** bottom) of the brain of an upstream migrating *G. australis*. In the case of the olfactory bulbs and the telencephalic vesicles, these were defined as parallel or perpendicular lines to the *Fissura circularis* (*fc*), which is highlighted with a discontinuous line in the telencephalon. The limit of the octavo-trigeminal and gustatory areas was defined by a line running parallel to the posterior end of the head of the eighth nerve (white arrow). **(B)** The same measurements were performed in the pineal organ after it was dissected and separated from the remainder of the brain. OB: olfactory bulbs, Te: telencephalic vesicles, PO: pineal organ, OT: optic tectum, OCT: octavo-trigeminal area, Gus: gustatory area. Scale bars = 1 mm.

Age Determination

The approximate age of the ammocoete samples was estimated from length-frequency histograms for larval and metamorphosing representatives of *G. australis* (Potter et al., 1980; Potter and Hilliard, 1986). Age of adult stages was inferred from the timing of the upstream migration and sexual maturation (Potter et al., 1983).

Data Analysis

All analyses were performed using the open source software R (R Core Team, 2013). The complete dataset was divided into two subsets, one containing body and brain mass ($n = 32$) and the other containing total brain and brain structure volume estimates ($n = 39$).

Linear Models

For brain and brain structure scaling analyses, each data set was $\log_{10}$ transformed to improve normality prior to analysis, after being multiplied by an arbitrary factor (10 and 1000, respectively), in order to obtain positive values of the variables following $\log_{10}$ transformation. We conducted similar analyses on both datasets: we fitted least squares regressions within and between stages, and performed analyses of covariance (ANCOVA), with brain mass as the response variable, body mass as the covariate, and stage as a factor for the brain and body mass comparisons. In the case of the brain structures, total brain structure volume was compared to total brain volume minus total structure volume as a covariate. This was done to account for the bias that exists when a brain subdivision is scaled against total brain mass (which includes the subdivision of interest) (Deacon, 1990; Iwaniuk et al., 2010). To control for similarity within the larval or adult phases of the life cycle, stages were combined in "stage 1" (no combination), "stage 2" (all ammocoetes grouped together), "stage 3" (all adults grouped together), "stage 4" (all ammocoetes grouped together, downstream and upstream migrants grouped together),

"stage 5" (all ammocoetes grouped together, upstream migrants and maturing adults grouped together), and "stage 6" (all ammocoetes grouped together, all adults grouped together) (See Supplementary Table 2). Linear models were fitted to each of these factors and the linear assumptions for each were checked using the R package glvla (Pena and Slate, 2014); valid linear models were then compared and selected using the second-order Akaike Information Criterion (AICc); If the best model had a AICc value indistinguishable from the following model(s), they were averaged using multi-model inference methods contained in the R package MuMIn (Barton, 2014), and the relative importance of the factor in the resulting model was used as a criterion for selection. Tukey *Post-hoc* tests were used to detect differences between groups in the selected models.

Principal Component Analysis

We also used a multivariate approach to determine the clustering of the samples in multidimensional space and characterize the patterns of brain organization of *G. australis* at each point of the life cycle. Principal component analysis (PCA) was performed using relative volume of each structure, calculated as a fraction of the sum of the volume of all six brain structures measured within a specimen (Wagner, 2001; Lisney et al., 2007). Structure proportions were normalized using the arcsine square root transformation previous to analysis. PCA was run using the autocovariance matrix and the singular value decomposition method for better numerical accuracy.

Results

Brain Scaling

The brain of *G. australis* shared similar characteristics with those of other species of lampreys (**Figure 3**) (Wicht, 1996; Nieuwenhuys and Nicholson, 1998). Our analysis of the scaling of brain and body mass in *G. australis* at successive stages of development revealed that the brain and body have different scaling patterns during ontogeny (**Figure 4A**). Body mass grows at a higher rate than brain mass in both the adult phase and the analyzed period of the larval phase, a trend that is interrupted during metamorphosis (**Figure 4A**, arrows), where body mass was similar between downstream migrants and the latest ammocoete stage (Two-tailed Welch t-test, $T = 1.98$, $p = 0.201$); however, brain mass was significantly higher in downstream migrants as compared to ammocoetes IV (One-tailed Welch t-test, $T = 7.8$, $p = 0.037$).

According to the second-order Akaike information criterion, the best model of brain mass as a function of body mass occurred when stage 2 was used as a factor, grouping all ammocoetes together (Supplementary Table 3). We fitted stage-specific (intraspecific) regressions to each of these groups, whose slopes varied across ontogeny (**Figure 4B**); all groups showed intraspecific negative allometry of brain mass with body mass. The highest rate of brain growth was reached at the larval phase ($\alpha = 0.47$), followed by downstream and upstream migrants (Supplementary Table 4), while the period of regression of body mass in the course of maturation was accompanied by a steep reduction of brain mass ($\alpha = 0.90$). We also defined an ontogenetic linear regression as the line of best fit between all specimens, where most of the groups had large deviations from the predicted values of brain mass (**Figure 4C**), indicating that brain mass does not scale linearly with body mass at all stages in the life cycle of *G. australis*. These two sets of regressions were combined in an analysis of covariance (ANCOVA), the results of which are illustrated in **Figure 4D**. These data show that both stage 2 and body mass are significant when explaining the observed variance of brain mass (ANCOVA, $p < 0.001$), and no significant interaction between factor (stage 2) and covariate (body mass) is found, indicating no significant differences in the

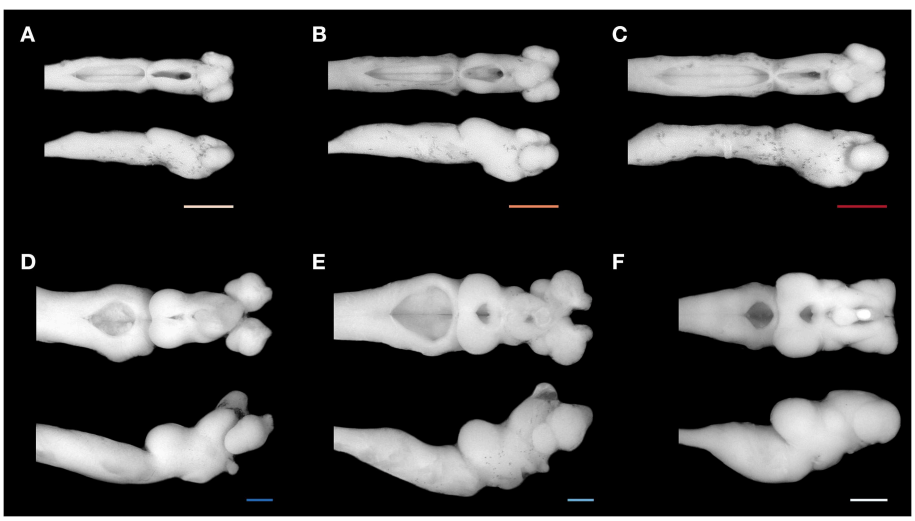


FIGURE 3 | Brain of *Geotria australis* during ontogeny. A representative brain of each stage studied is shown in a dorsal (top) and lateral view (bottom): **(A)** second age class ammocoete, **(B)** third age class ammocoete, **(C)** fourth age class ammocoete, **(D)** maturing adult, **(E)** upstream migrant, and **(F)** downstream migrant. Note the marked difference between the brain of a late ammocoete and a downstream migrant **(C,F)**. Scale bars = 1 mm.

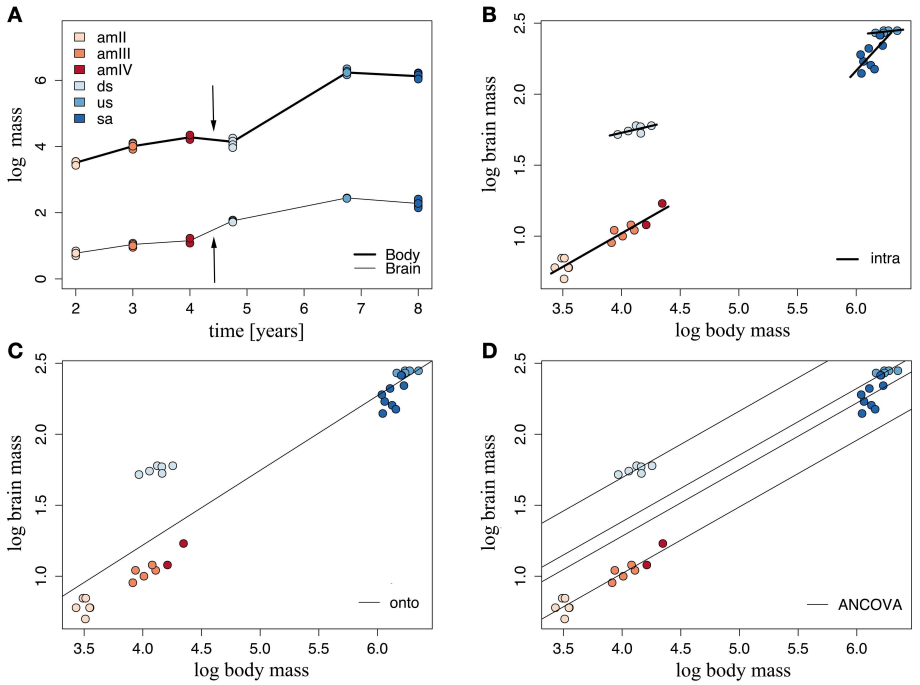


FIGURE 4 | Brain and body growth vary during the ontogeny of *Geotria australis*. **(A)** Brain and body mass growth traced over time. Arrows mark the period of metamorphosis. **(B)** Intraspecific linear regressions, **(C)** Ontogenetic regressions, and **(D)** Linear regressions fitted for each stage after an ANCOVA analysis. For the values of the parameters of these regressions, refer to Supplementary Table 4. amII, second year class ammocoetes; am III, third year class ammocoetes; amIV, fourth year class ammocoetes; ds, downstream migrants; us, upstream migrants; sa, spawning adults.

slopes calculated for each group in the stage-specific regressions. The ANCOVA calculated a common slope, with a similar value to the slope obtained in the intraspecific regression of ammocoetes, and different intercepts for each group (See Supplementary Table 4), which represent differences in relative brain mass between groups. The Tukey *Post-hoc* test showed significant differences between all groups of stage 2 ($p < 0.001$); downstream migrants had the highest intercept, demonstrating an increase in relative brain mass at this stage.

Scaling of Brain Structures

The analyzed brain structures showed different patterns of growth during the life cycle of *G. australis*. Ontogenetic regressions of total structure volume against total brain volume minus structure volume (hereafter referred to as brain volume) were fitted to each of the structures analyzed and their parameters are tabulated in Supplementary Table 5. A general trend between these regressions was the large deviations from the expected values shown by the downstream migrants, which were positive for the telencephalon and the optic tectum, but negative in the case of the pineal organ, the octavo-trigeminal area and the gustatory area.

The olfactory bulb was the only structure where the observed values fitted the expected values closely in all the stages, supporting a linear scaling of this structure with total brain throughout ontogeny (**Figure 5A**). Remarkably, the olfactory bulbs showed the steepest hyperallometric growth reported in this study ($\alpha = 1.27$), generating highly developed olfactory bulbs in upstream migrants and maturing adults. The pineal organ and the octavo-trigeminal area also showed a significant linear fit with total brain volume, as shown in Supplementary Table 5, although this was not the best model for these structures (see below).

Similar to the olfactory bulbs, the telencephalic hemispheres showed a close fit to brain volume in most stages, but because of the high heteroscedasticity in the values of maturing adults, the linear assumptions were violated in this case and in other tested linear models of the telencephalic hemispheres (results not shown). Nevertheless, we found that these assumptions were valid when fitting the telencephalic volume with the volume of the olfactory bulbs, and thus in this case total olfactory bulbs volume was used as covariate in the ANCOVA analysis. The best model for the telencephalic hemispheres included stage 6 as a factor (**Figure 5B**). This structure showed linear growth with the olfactory bulbs along the larval phase and an increase in size after metamorphosis, which is maintained throughout the adult phase of the life cycle. However, only a marginal difference was detected between ammocoetes and adults (Tukey *Post-hoc* test, $p = 0.091$).

The best models for the pineal organ and the gustatory area had stage 2 as factor, whereas for the octavo-trigeminal area it was stage 1 and for the optic tectum it was stage 4 (Supplementary

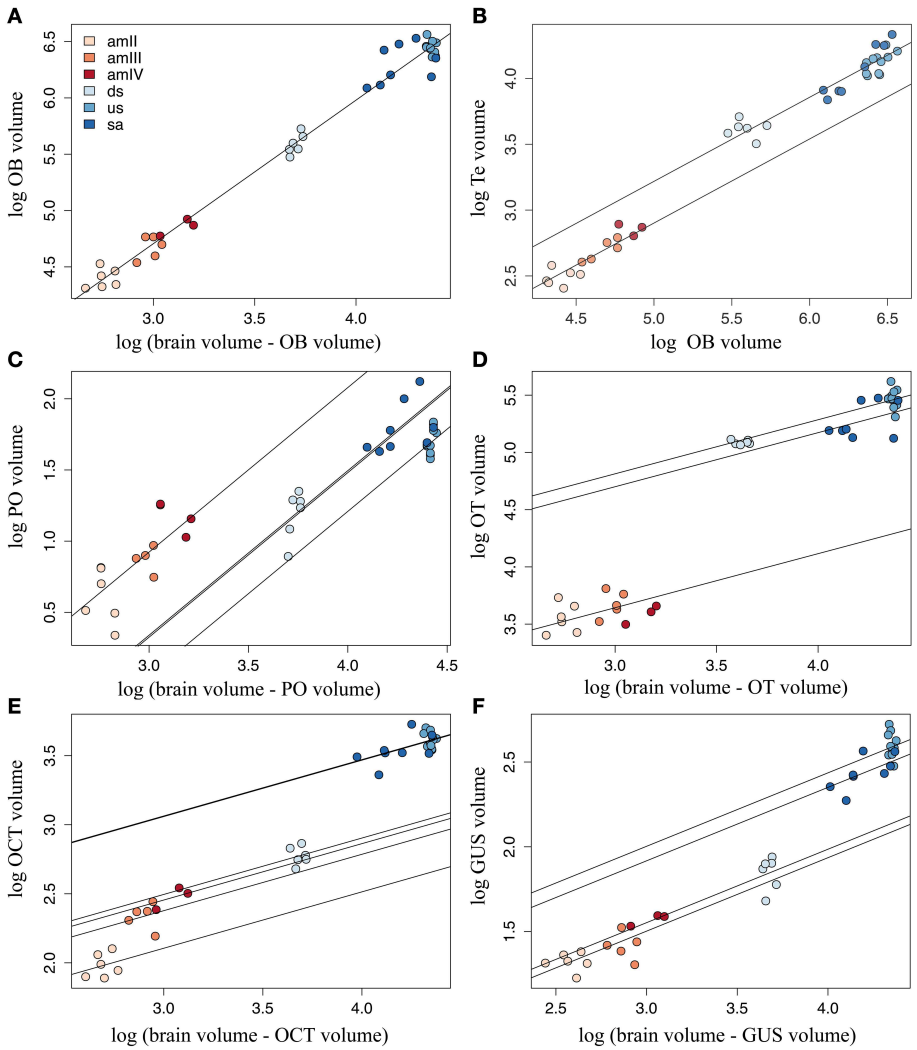


FIGURE 5 | Calculated regression lines after ANCOVA. Best linear models are plotted for each structure, showing the differences in scaling of each structure to the rest of the brain: **(A)** olfactory bulbs (OB), **(B)** telencephalic hemispheres (Te), **(C)** pineal organ (PO), **(D)** optic tectum (OT), **(E)** octavo-trigeminal area (OCT), and **(F)** gustatory area (GUS). For the values of the parameters of these models, refer to Supplementary Table 5. amII, second age class ammocoetes; amIII, third age class ammocoetes; amIV, fourth age class ammocoetes; ds, downstream migrants; us, upstream migrants; sa, spawning adults.

Table 3). The calculated slope for the pineal organ in the ANCOVA was higher than in the ontogenetic regression, and ammocoetes had the highest intercept (**Figure 5C**). We found no significant differences between ammocoetes, downstream and upstream migrants, but the pineal organ in maturing adults was significantly different from that of downstream migrants, although only marginally different from upstream migrants (Tukey *Post-hoc* test, $p = 0.017$ and 0.053, respectively). The corrected slope for the optic tectum showed two markedly slow phases of growth, larval and adult, with a significant difference in size between them (Tukey *Post-hoc* test, $p < 0.05$; **Figure 5D**); the optic tectum of maturing adults was significantly reduced compared to downstream and upstream migrants (Tukey *Post-hoc* test, $p < 0.05$), and not different from the optic tectum of ammocoetes (Tukey *Post-hoc* test, $p = 0.45$).

The volume of the gustatory area of the downstream migrants was significantly different to the other stages (Tukey *Post-hoc* test, $p < 0.05$), with a shallow slope ($\alpha = 0.43$). However, considering the value of the calculated intercepts in the ANCOVA of the gustatory area, the downstream migrants clustered with ammocoetes, whereas upstream migrants and maturing adults had higher values of intercepts (**Figure 5E**). This was also the case for the octavo-trigeminal area, where the volume in downstream migrants was different from all the other stages (Tukey *Post-hoc* test, $p < 0.05$) and their volume was closer to ammocoetes than to adults although, in contrast to all other structures, we found that in this area the ammocoetes were best fitted as separate groups, where the second age class ammocoetes had a smaller intercept than other larval stages (Tukey *Post-hoc* tests: amIII, $p = 0.020$; amIV, $p = 0.083$; **Figure 5F**). Some maturing

adults possessed a relatively higher octavo-trigeminal area than upstream migrants, consistent with the modifications of the oral disc and the appearance of the gular sac in this period (Potter et al., 1983; Neira, 1984). However, we did not observed significant differences between these groups. Our results also showed no consistent differences between male and female lampreys in any structure (results not shown).

Multivariate Analysis and Stage Clustering

The principal component analysis performed on the correlation matrix of the relative size of the six brain structures measured in this study provided a clear separation in the multidimensional space of the two phases of the life cycle of *G. australis*. The relative loadings of the first four components and their relative importance are given in **Table 1**. The first two components explained 93.3% of the overall variance and their scores are plotted in **Figure 6**. The first component (PC1) reflects the high loadings for the optic tectum and gustatory area, and secondarily in the olfactory bulbs, separating larvae, which had a relatively large gustatory area and pineal organ, from adults, which had relatively larger optic tecta, olfactory bulbs and telencephalic hemispheres. Similarly, the second component (PC2) separated younger and older individuals within a phase, where older individuals had relatively larger olfactory bulbs and octavo-trigeminal areas than younger individuals in both phases of the life cycle.

Discussion

Lampreys experience very different behavioral phases during the life cycle, from a microphagous sedentary mode to an active parasitic mode. This study characterized the growth of the brain (encephalization) during the life cycle of *G. australis*, focusing on the scaling between brain and body throughout ontogeny and testing the hypotheses that the vast transitions in behavior and environment are reflected in differences in both encephalization and the relative development of major brain subdivisions.

The changes occurring in the nervous system of lampreys during ontogeny have attracted the attention of many comparative neurobiologists, who have shown extensive morphological and physiological modifications of the peripheral and central nervous system, such as the development of the visual system (Kennedy and Rubinson, 1977; Kosareva, 1980; De Miguel and Anadon, 1987; Rubinson, 1990; Fritzsch and Northcutt, 1993b; Pombal et al., 1994; Davies et al., 2007; Villar-Cheda et al., 2008). However, in spite of the multiple studies quantifying these changes throughout the life cycle (Tamotsu and Morita, 1986; De Miguel and Anadon, 1987; Currie and Carlsen, 1988; Melendez-Ferro et al., 2003; Vidal Pizarro et al., 2004; Antri et al., 2006), an overall view of the pattern of development of the brain and its organization, including larval and adult phases, has been absent until now.

Brain Scaling

The description of the changes in encephalization during the life cycle of jawless fishes will improve our current understanding brain development at multiple levels. Previous interspecific studies in agnathans have differed on the scaling relationship between brain size and body size of lampreys, ranging from 0.23 (Ebinger et al., 1983) to 0.56 (Platel and Vesselkin, 1988). In addition to discrepancies in the value of the scaling exponent, both studies suffered from low sample sizes, with data on only three (Ebinger et al., 1983) and two (Platel and Vesselkin, 1988) species, out of 41 currently recognized species of lampreys (Potter et al., 2015). This discrepancy in the scaling exponent requires improved resolution, as one value classifies lampreys as being far less encephalized than other gnathostomes, with a slow rate of growth of the brain in relation to the body ($\alpha = 0.23$),

TABLE 1 | Results of the principal component analysis for the first four components.

Importance of components	PC1	PC2	PC3	PC4
Standard deviation	0.189	0.093	0.046	0.031
Proportion of the variance	0.749	0.183	0.045	0.021
Cumulative proportion	0.749	0.933	0.978	0.998
RELATIVE LOADINGS				
OB	0.313	0.523	−0.710	0.150
Te	0.125	−0.044	0.007	−0.868
PO	−0.094	−0.089	0.084	−0.101
TO	0.666	−0.472	0.193	0.345
OCT	−0.186	0.576	0.584	0.217
GUS	−0.633	−0.403	−0.332	0.218

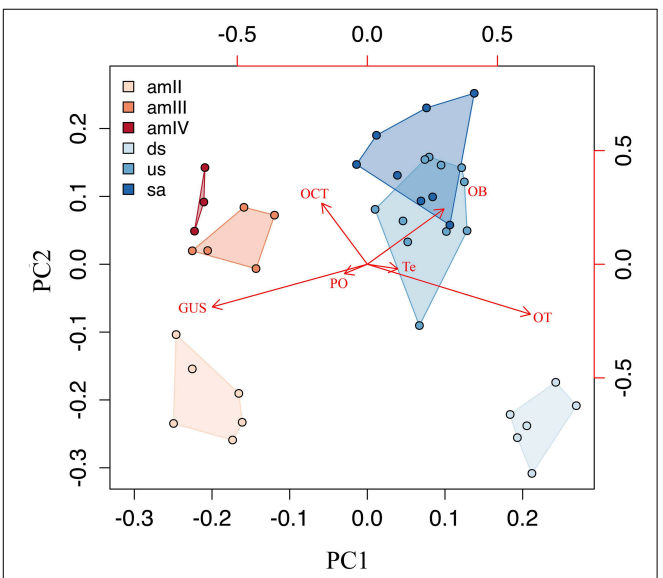


FIGURE 6 | A scatterplot of principal components PC1 and PC2. Principal component analysis, representing the major changes in the composition of the brain during the life cycle. OB, olfactory bulbs; Te, telencephalic hemispheres; PO, pineal organ; OT, optic tectum; OCT, octaval-trigeminal area; GUS, gustatory area; amII, second age class ammocoetes; amIII, third age class ammocoetes; amIV, fourth age class ammocoetes; ds, downstream migrants; us, upstream migrants; sa, spawning adults.

while the other places this group within the known range of the interspecific variation in the scaling exponent between most vertebrate groups ($\alpha = 0.56$), which usually falls between 0.5 and 0.6 (Striedter, 2005). Similarly, no consensus has been reached with regards to the intraspecific scaling exponent in the sea lamprey *Petromyzon marinus*, which ranges from −0.04 (Ebinger et al., 1983) to 0.56 (Platel and Delfini, 1986). However, given the dramatic shifts that occur throughout the life history of lampreys, these published values for brain scaling are likely to be highly dependent on when in the life cycle the brains were sampled. In fact, this study shows that, as lampreys advance in their upstream migration, they lose both body and brain mass at different rates, which is reflected in a higher intraspecific scaling factor in maturing adults (**Figure 4**). This variation between early and late upstream migrants may explain previously reported discrepancies in the intraspecific allometric slope in *P. marinus*. Nonetheless, it is possible that the observed differences in relative brain mass may also be related to intraspecific variation between separate populations (Gonda et al., 2011) or according to mating strategies (Kolm et al., 2009), which have also been described in lampreys (Hume et al., 2013).

The ontogenetic scaling of brain and body mass in other basal vertebrate groups, such as teleost fishes, has shown that the larvae of both metamorphic (Bauchot et al., 1979; Tomoda and Uematsu, 1996; Wagner, 2003; Sala et al., 2005) and non-metamorphic fishes (Iribarne and Castelló, 2014) exhibit allometric scaling between brain and body size in the early post-hatching development phase, which may be equivalent to the linear phase of growth reported for ammocoetes in this study. However, in the case of metamorphic fishes, such as the rainbow trout *Oncorhyncus mykiss* or the Japanese eel *Anguilla japonica*, there is no clear evidence of an increase of encephalization associated with metamorphosis (Bauchot et al., 1979; Tomoda and Uematsu, 1996), as our results suggest for lampreys, but constitutes an interesting point that warrants further investigation and should be an area of future study.

Teleost fishes possess continuous growth of both the body and the nervous system throughout life (Bauchot et al., 1979; Leyhausen et al., 1987), as opposed to amniotes where brain growth plateaus before the animal reach its final body size (reviewed in Striedter, 2005), although there are some exceptions (Ngwenya et al., 2013). Yet in lampreys, our results and previous records on *P. marinus* (Ebinger et al., 1983) suggest that, in early upstream migrants (end of the parasitic phase), brain growth may have actually reached a plateau, given the low intraspecific scaling factor found at this point of the life cycle (**Figure 4B**: $\alpha = 0.09$ for *G. australis*, $\alpha = -0.04$ for *P. marinus*), although these values were not statistically significant in either study. In addition, we found evidence that a relative reduction in brain mass occurs in parallel with the typical reduction of body mass in maturing lampreys (Potter et al., 1983; Paton et al., 2011), which has not been previously shown in other ontogenetic studies of brain scaling in vertebrates. Even though complex behavior is generally associated with larger brains (reviewed by Striedter, 2005), lampreys still exhibit sophisticated behaviors, such as nest construction, in this period (Hardisty and Potter, 1971; Sousa et al., 2012; Johnson et al., 2015).

Brain growth in vertebrates has been described as the result of several processes, including cell growth and the addition and elimination of cells (Pirlot and Bernier, 1991; Candal et al., 2005; Bandeira et al., 2009; Fu et al., 2013; Boyd et al., 2015). In lampreys, neuro- and glio-genesis are restricted to ventricular proliferative zones in late embryos and early to mid larval stages (Vidal Pizarro et al., 2004; Villar-Cheda et al., 2006; Guerin et al., 2009) and, although adult neurogenesis is widespread in other basal vertebrate groups (Kaslin et al., 2008), it is considered mostly absent in lampreys (Villar-Cheda et al., 2006; Kempermann, 2012). Taken together, these results suggest that brain growth from late ammocoetes onwards is mainly due to the addition of glia, cell growth, and the establishment of new synapses that contribute to the formation of plexiform tissue or neuropil, as suggested previously for lampreys (Rovainen, 1979, 1996).

Scaling of Brain Structures

Transitions in habitat and behavior are common during the development of aquatic vertebrates, even if they do not undergo a metamorphic stage, such as recruitment of fish larvae (Kingsford et al., 2002; Kotrschal et al., 2012; McMenamin and Parichy, 2013) and the use of nursery areas in sharks (e.g., Bethea et al., 2004; Heupel and Simpfendorfer, 2011). Usually these transitions are accompanied by *ad-hoc* sensorimotor specializations (Brandstätter and Kotrschal, 1990; Montgomery and Sutherland, 1997; Lisney et al., 2007; Lecchini et al., 2014). Similarly, adults of both bony and cartilaginous fishes, as well as other vertebrates, possess well-developed adaptations to their ecological niche, which are generally reflected in their nervous system as a variation in the relative size of brain subdivisions (Kotrschal and Palzenberger, 1992; Gonzalez-Voyer et al., 2009; Gonzalez-Voyer and Kolm, 2010; Yopak, 2012). Surprisingly, the relative size of these brain subdivisions appear to be constant between species of parasitic lampreys, despite the diverse aquatic niches in which they inhabit (Renaud, 2011; Potter et al., 2015). We found that the optic tectum and olfactory bulbs in adults of *G. australis* comprise similar proportions of the brain to that of *P. marinus* (Platel and Delfini, 1986) and other species of lampreys (Platel and Vesselkin, 1989), concordant with the lack of appreciable neuroanatomical differences in the brain between lamprey species, as reported previously (Platel and Vesselkin, 1989; Nieuwenhuys and Nicholson, 1998). However, we consider that more species of lampreys needs to be examined, including those with alternative life style strategies, such as parasitic and non-parasitic paired species of lampreys, to have a wider perspective of the diversity found in the nervous system of extant agnathans.

Olfactory Bulbs

It has been suggested that the level of variation in the relative size of the major brain subdivisions may occur in particular structure in a modular or mosaic fashion (Barton and Harvey, 2000), or with a concerted pattern of allometric scaling (Finlay and Darlington, 1995). It has recently been shown that most major brain areas in cartilaginous fishes scale with a characteristic slope that may be conserved across other vertebrates, including

mammals (Yopak et al., 2010). One notable exception is found in the olfactory bulbs, which maintain a level of statistical independence from total brain size in a range of vertebrate groups (Finlay and Darlington, 1995; Gonzalez-Voyer et al., 2009; Yopak et al., 2010, 2015). At the ontogenetic level, however, our analysis of the scaling of the olfactory bulbs shows the opposite pattern, whereby the olfactory bulbs scale very tightly with total brain size, with a highly hyperallometric growth (**Figure 5A**).

Multiple functional hypotheses have been proposed to explain the relative size of the olfactory bulbs (reviewed in Yopak et al., 2015), including the relationship of olfactory cues with navigation, which may play an important role in lampreys while finding a host or on their way back to rivers for the spawning run (Siefkes et al., 2003; Johnson et al., 2005, 2009; Sorensen et al., 2005; Wagner et al., 2009). The olfactory spatial hypothesis predicts that the size of the olfactory bulbs should covary with navigational ability, which is supported by the olfactory input to the hippocampus (Jacobs, 2012). The statistical independence of the olfactory bulbs is then substantiated by the fact that the olfactory bulbs, the hippocampus, and other associated areas of the telencephalon do not scale as tightly with brain size as do other brain subdivisions (Finlay and Darlington, 1995; Finlay et al., 2001; Gonzalez-Voyer et al., 2009; Yopak et al., 2010) and can vary across mammalian taxa depending on the influence of olfactory cues in their behavior (Reep et al., 2007). If these theories can be applied in the context of the lamprey life cycle, we would therefore expect that, should homologous olfactory areas exist in the telencephalon of *G. australis*, they would also scale isometrically with the rest of the brain in this group during ontogeny. Early descriptions of the telencephalon of the lamprey and later hodological evidence have suggested the presence of a hippocampal primordium or medial pallium (Johnston, 1912; Northcutt and Puzdrowski, 1988; Polenova and Vesselkin, 1993; Northcutt and Wicht, 1997). However, scaling of these telencephalic structures have not been studied in agnathans at any level, and even the existence of a medial pallium is disputed by neuroanatomical descriptions based on molecular markers (Pombal and Puelles, 1999; Weigle and Northcutt, 1999; Pombal et al., 2011). Considering that interspecific scaling of the olfactory bulbs has not yet been described in jawless fishes, the available evidence does not permit any definitive conclusions to be made with regard to differences found in the scaling of the olfactory bulbs between lampreys and other vertebrates.

An alternative explanation of the involvement of olfaction in navigation in lampreys is the hypothesis of dual olfaction, which assumes parallel processing of distinct sets of molecules or environmental odors by the main olfactory system and pheromones by the vomeronasal system, following independent pathways in the brain, and acting synergistically in the regulation of olfactory-guided behaviors (reviewed in Suárez et al., 2012). In lampreys, two anatomically distinct sets of olfactory epithelia have been described that show different patterns of central projections, which suggests the existence of a precursor of the vomeronasal system in this group (Ren et al., 2009; Chang et al., 2013). This accessory olfactory system is tightly coupled to motor areas of the brain, constituting an unusual motor system in vertebrates, which is capable of eliciting swimming movements after olfactory stimulation with both naturally occurring odors and pheromones (Derjean et al., 2010). Since lampreys can detect very low (subpicomolar) concentrations of pheromones (Sorensen et al., 2005), this system may be employed in navigation and other behaviors involving pheromone perception, such as searching for a natal river environment to spawn (Siefkes et al., 2003; Johnson et al., 2005, 2009; Sorensen et al., 2005; Wagner et al., 2009). However, whether these differential central projections vary interspecifically and affect the relative size of the olfactory bulbs and/or a tight coupling between development of the olfactory bulbs and motor areas in the brain is unknown and requires further research.

The Telencephalic Hemispheres

Interspecific studies of the scaling of major brain subdivisions have shown that areas of the brain associated with behavioral and motor complexity, e.g., telencephalon and cerebellum, enlarge disproportionately as brain size increases in a range of vertebrates (Finlay and Darlington, 1995; Finlay et al., 2001; Pollen et al., 2007; Yopak et al., 2010). In lampreys, the everted portion of the telencephalon considered in this study (the cerebral hemispheres or telencephalic hemispheres) can be regarded as the multimodal sensorimotor integration center of the telencephalon, providing a neural substrate for orientation movements of the eyes, trunk, and oral movements, due to direct efferent projections to brainstem motor centers and the optic tectum, in a similar fashion to motor control systems of amniote vertebrates (Ericsson et al., 2013; Grillner and Robertson, 2015; Ocaña et al., 2015). The telencephalic hemispheres are also the main target of secondary olfactory projections from the lateral olfactory bulb, which, in turn, receives its primary afferents from the main olfactory epithelium (Northcutt and Puzdrowski, 1988; Northcutt and Wicht, 1997; Ren et al., 2009; Derjean et al., 2010). Therefore, it is not surprising to find a tight scaling relationship between this structure and the olfactory bulbs ($R^2 = 0.987$). In addition, this telencephalic area receives afferent fibers from the dorsal thalamus, possibly relaying visual and other sensory input that converge on this thalamic area (Polenova and Vesselkin, 1993; Northcutt and Wicht, 1997). Although not significant, there is some evidence of differences in the size of the telencephalic hemispheres between larvae and adults (Tukey *Post-hoc* test, $p = 0.091$), which may be due to the increase of secondary sensory fibers terminating in this area, as both the primary olfactory system (Vandenbossche et al., 1995; Villar-Cheda et al., 2006) and the primary visual projections to the dorsal thalamus (Kennedy and Rubinson, 1977; Kosareva, 1980) develop during metamorphosis. Despite the various studies on the pallial telencephalon of lampreys, no consensus has been achieved yet in relation to the homology of this area with the pallium of other vertebrates (Northcutt and Puzdrowski, 1988; Nieuwenhuys and Nicholson, 1998; Pombal et al., 2009).

The Pineal Organ

The pineal complex in lampreys is formed by the pineal and the parapineal organs (Eddy and Strahan, 1970; Puzdrowski and Northcutt, 1989; Pombal et al., 1999; Yáñez et al., 1999), which participate in non-visual photo-perception and neuroendocrine

control of the circadian rhythms in these animals, as it does in a range of vertebrates (Ekström and Meissl, 1997, 2003; Vernadakis et al., 1998). The pineal organ has also been documented in extinct agnathans, where it was similar in relative size to that of contemporary ammocoetes (Gai et al., 2011), suggesting that non-visual light perception was also highly developed in these extinct groups. The observed morphological and physiological variability of this organ in tetrapods has been linked to latitudinal distribution of the species (Ralph, 1975), nocturnality (Bhatnagar et al., 1986; Haldar and Bishnupuri, 2001), and habitat depth in demersal fishes (Wagner and Mattheus, 2002; Bowmaker and Wagner, 2004), although none of these factors fully explained the variability found in the size and morphology of this organ across species.

The best model for the pineal organ described three distinctive periods of growth in the life cycle of *G. australis*. First, there was consistent hyperallometric growth throughout the larval phase; in the second period, during early adult life, including the marine parasitic phase, we observed that the growth of this organ plateaus after metamorphosis, where the size of the pineal organ of ammocoetes was not significantly different to that of downstream or upstream migrants, opposite to what was observed in the other brain structures; and third, we found a relative increase in the size of the pineal organ during sexual maturation. A similar pattern of growth has been documented in the pineal organ of the arctic lamprey *Lethenteron camtschaticum* (Tamotsu and Morita, 1986). The larval phase and sexual maturation periods anticipate important milestones in the ontogeny of lampreys, such as the onset of metamorphosis and spawning, both of which likely depend on the timing of circadian rhythms (Freamat and Sower, 2013). In this regard, it was shown that metamorphosis was prevented with pinealoctomy in *G. australis* and other species (Eddy and Strahan, 1968; Cole and Youson, 1981), and maturation was delayed in adults of the river lamprey *Lampetra fluviatilis* after the same procedure (Eddy, 1971).

The Optic Tectum

In lampreys and other non-mammalian vertebrates, the optic tectum is the main primary visual center of the brain, receiving extensive topographic retinal (retinotopic) projections to the superficial layers (Butler and Hodos, 1996; Iwahori et al., 1999; De Arriba and Pombal, 2007; Jones et al., 2009). Electroreceptive and other sensory input also converge onto this tectal map (Bodznick and Northcutt, 1981; Ronan and Northcutt, 1990; Robertson et al., 2006), where the relevance of salient stimuli can be assessed, as in other vertebrates (Karamian et al., 1966, 1984; Pombal et al., 2001; Gruberg et al., 2006; Kardamakis et al., 2015), leading to orienting movements of the eye, head and trunk (Saitoh et al., 2007; Ocaña et al., 2015).

Ontogenetic comparisons of the relative size of the optic tectum have been documented in several species of elasmobranchs (Lisney et al., 2007) and teleost fishes (Brandstätter and Kotrschal, 1990; Kotrschal et al., 1990; Wagner, 2003), and have shown a shift from an initially well-developed visual system, followed by a relative reduction in the size of the optic tectum and a corresponding increase in other sensory brain areas, such as those that process olfactory or lateral line input, as the animal matures. This change in brain organization has been associated with shifts in ecological niche, from a well-lit environment in epipelagic fish larvae or nurseries of juvenile elasmobranchs to a different primary habitat as adults. In contrast to these groups, we report an opposite shift in brain organization. In ammocoetes of *G. australis,* the optic tectum underwent moderate growth with total brain size ($\alpha = 0.47$; **Figure 5D**). In fact, this structure remains mostly undifferentiated and poorly layered during most of the larval phase in lampreys (Kennedy and Rubinson, 1977; De Miguel and Anadon, 1987; De Miguel et al., 1990) and only the central retina is differentiated (Meyer-Rochow and Stewart, 1996; Villar-Cheda et al., 2008). The major growth of the optic tectum occurs in conjunction with the development of the adult eye, in a rapid process that starts at the end of the larval phase and continues during the initial stages of metamorphosis (Potter et al., 1980; De Miguel and Anadon, 1987). Indeed, it is only at the end of the larval phase that the typical retinotopic projections found in adults reach the optic tectum (Jones et al., 2009; Cornide-Petronio et al., 2011). Soon after metamorphosis (downstream migrants), the relative size of the optic tectum is more similar to that of adults than ammocoetes (Supplementary Table 5, **Figure 5D**).

This rapid development of the visual system explains the lack of a linear fit of the optic tectum in the ontogenetic scaling of this structure with the rest of the brain. We expect that this fast switch from non-visual to visual perception will also affect the scaling of other visual areas of the brain receiving primary retinal input, such as the dorsal thalamus, and that it may be less pronounced in non-visual areas receiving retinal projections, such as the hypothalamus and pretectal area, which are already developed in ammocoetes, where they participate, for example, in non-visual reflexes (De Miguel and Anadon, 1987; Ullen et al., 1995, 1997; Jones et al., 2009). Nevertheless, the scaling of these visual and non-visual areas of the brain has yet to be studied.

Our results suggest that vision may be important during the parasitic phase, reflected in the high development of the optic tectum during metamorphosis. However, the significant reduction in the size of the optic tectum in maturing adults, which is corroborated with reports of eye degeneration during the spawning run (Applegate, 1950), supports previous evidence that vision is not important in lampreys during their upstream migration (Binder and McDonald, 2007; Johnson et al., 2015).

Medulla Oblongata

Interspecies comparisons in gnathostomes and agnathans have shown that the size of the rhombencephalon, i.e., the medulla oblongata plus the cerebellum, is well-predicted from total brain size in both groups (Ebinger et al., 1983; Yopak et al., 2010), although in lampreys only cerebellum-like structures can be identified (Weigle and Northcutt, 1998; Northcutt, 2002; Montgomery et al., 2012). When comparing brain subdivisions, the medulla oblongata had the lowest scaling factor in cartilaginous fishes (Yopak et al., 2010), whereas it was the highest in agnathans (Ebinger et al., 1983). Indeed, the medulla accounts for approximately half of the total brain size in adult

lampreys (this study, Platel and Vesselkin, 1989), and even more in early larvae (Scott, 1887), although this is not as obvious in downstream migrants (see below). The medulla is the first to develop cranial nerves in lampreys (Kuratani et al., 1997; Barreiro-Iglesias et al., 2008) and maintains a relatively stable scaling relationship with total brain size during the later larval phase and even throughout metamorphosis (**Figures 5E, F**). However, there was a significant difference in the size of the octavo-trigeminal area between the second-age class ammocoetes and older stages (see intercepts in Supplementary Table 5), which may be related to the development of a number of the diverse sensory and motor systems located in this brain structure, as discussed previously.

The growth of the medulla oblongata during metamorphosis maintains a tight scaling relationship with total brain size in late ammocoetes, which supports previous findings that the motoneurons of the trigeminal nucleus in lampreys are conserved through metamorphosis, in spite of the massive replacement of muscle in the head during this period (Homma, 1978; Rovainen, 1996). This has also been documented in other metamorphic vertebrates, such as frogs (Alley and Omerza, 1998).

However, while several brain structures, e.g., the olfactory bulbs and the optic tectum, exhibit greater rate of growth during metamorphosis, both the octavo-trigeminal and gustatory areas grow with a slower rate during this phase, which is expressed as a lower proportion of this area compared to total brain volume in downstream migrants. Nonetheless, our results show a later growth phase of this subdivision during the parasitic phase, particularly of the octavo-trigeminal area, which may be associated with the development of the musculature of the ventilatory branchial basket and the oropharyngeal region, and to the scaling of other somatic and sensory functions as body size enlarges during the marine parasitic phase (Aboitiz, 1996; Rovainen, 1996; De Winter and Oxnard, 2001).

Neuroecology of the Life Cycle

Growth of the central nervous system in lampreys is a discontinuous process, with a variable rate of growth of both total brain and its subdivisions throughout life, which was expressed in the relative size of diverse brain structures in each phase of the life cycle (**Figure 6**). These patterns of brain organization may be interpreted as "cerebrotypes" (Clark et al., 2001; Iwaniuk and Hurd, 2005; Willemet, 2012, 2013), whereby similar patterns of brain organization exist in species that share certain lifestyle characteristics. In this case, different cerebrotypes may in fact exist within a species at different phases of the life cycle.

The ammocoetes of *G. australis* are less encephalized compared to young adults (downstream migrants), with brains that are characterized by a relatively large gustatory area and a highly developed pineal organ (**Figures 3**, **6**). The relative size of the octavo-trigeminal area is increased in late ammocoetes (**Figure 5E**), whereas the olfactory bulbs, telencephalic hemispheres and optic tectum were relatively small during the whole larval phase (this study, Scott, 1887). It is possible that these characteristics are related to the requirements of a sessile, burrower lifestyle and/or to filter-feeding specializations in this group. Patterns of brain organization of other filter-feeding vertebrates has been described previously, such as the basking shark *Cetorhinus maximus* and the whale shark *Rhincodon typus* (Kruska, 1988; Yopak and Frank, 2009), and mobulid rays (Ari, 2011), which similarly possess a relatively small telencephalon and mesencephalon (Kruska, 1988; Yopak and Frank, 2009). However, given the drastic differences in the ethology between filter feeding jawless and cartilaginous fishes, it is impossible to draw parallels between patterns of brain organization in these groups. Further research is required to determine the existence of common characteristics in brain organization associated with a filter-feeding lifestyle in lampreys.

In contrast to ammocoetes, adult parasitic lampreys are active swimmers who are highly encephalized and possess a battery of well-developed sensory systems during the adult phase, including vision and olfaction. Correspondingly, they also possess a relatively large telencephalon and olfactory bulbs, structures that may be important in navigation (Derjean et al., 2010; Ocaña et al., 2015), and a relatively large optic tectum, which participates in orientation movements and plays a role in visual processing (Saitoh et al., 2007; Kardamakis et al., 2015). Interestingly, some of these features, such high levels of encephalization and a well-developed optic tectum, have also been observed in many coastal-oceanic and pelagic species of both cartilaginous and bony fishes (Lisney and Collin, 2006; Yopak, 2012; Yopak et al., 2015), which may be related to the sensory requirements of the open water habitat across both jawed and jawless fishes.

Conclusions

We have employed a widely-used volumetric approach (Huber et al., 1997; Wagner, 2001; Gonzalez-Voyer et al., 2009; Yopak and Lisney, 2012; Lecchini et al., 2014) to quantify differences in the relative size of major brain structures during the ontogeny of lampreys. Our results demonstrate shifts in encephalization between larvae and adults, as well as considerable differences in the relative size of brain subdivisions. Taken together, these shifts in brain organization may reflect the sensory requirements of this species at each stage of the life cycle. The inclusion of data of the growth of the brain and its subdivisions in embryonic, prolarva, and early larval stages of ammocoetes, metamorphic, as well as individuals sampled during the parasitic phase, will provide a more comprehensive insight of the growth of the brain and body during the life cycle of lampreys and eventually allow the use of alternative mathematical functions to describe the process of growth in each phase (i.e., Gompertz models, e.g., Calabrese et al., 2013).

It is yet to be determined whether this pattern of brain development is conserved in other species of lampreys, but we anticipate that it is, based on how conserved the life cycle is in this group (Potter et al., 2015), which could explain the reported homogeneity of the central nervous system between species of lampreys. Further studies on the changes in the brain of lampreys throughout ontogeny will contribute to the understanding of the evolution of the brain in agnathans and across vertebrates.

Author Contributions

SC, NH, IP, and CS contributed to the conception, RW and CS acquired the data, KY and CS designed the analyses and interpreted the data. CS drafted the article, and all authors collaborated in its revision.

Acknowledgments

This work was supported by an Australian Research Council Discovery Grant (DP120102327) to SC, UWA SIRF, UIS, and UIS Top Up Scholarships to RW, and UWA SIRF and CONICYT Becas Chile Scholarships to CS. We thank Dr. Maik Kschischo from University of Applied Sciences Koblenz for his advice on growth curves, and Dr. Evelyn Habit from the University of Concepcion for kindly donating samples for this study. We also thank Dr. Macarena Faunes from the University of Auckland and Dr. Howard Gill from Murdoch University for their critical review of the work, and the reviewers who helped to improve a previous version of this article. We are also grateful to Mr. Helios Lara for adapting the illustration on the life cycle of *Geotria australis*.

Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnins.2015.00251

References

Aboitiz, F. (1996). Does bigger mean better? Evolutionary determinants of brain size and structure. *Brain Behav. Evol.* 47, 225–235. doi: 10.1159/000113243

Alley, K. E., and Omerza, F. F. (1998). Reutilization of trigeminal motoneurons during amphibian metamorphosis. *Brain Res.* 813, 187–190. doi: 10.1016/S0006-8993(98)00980-9

Antri, M., Cyr, A., Auclair, F., and Dubuc, R. (2006). Ontogeny of 5-HT neurons in the brainstem of the lamprey, *Petromyzon marinus*. *J. Comp. Neurol.* 495, 788–800. doi: 10.1002/cne.20910

Applegate, V. C. (1950). Natural history of the sea lamprey, *Petromyzon marinus*, in Michigan. *U. S. Fish Wildlife Serv. Spec. Sci. Rep. Fish.* 55, 1–237.

Ari, C. (2011). Encephalization and brain organization of mobulid rays (Myliobatiformes, Elasmobranchii) with ecological perspectives. *TOANATJ* 3, 1–13. doi: 10.2174/1877609401103010001

Ariëns Kapper, J. (1936). Brain-bodyweight relation in human ontogenesis and the "indice de valeur cérébrale" of Anthony and Coupin. *Proc. R. Neth. Acad. Arts Sci.* 39, 1019–1028.

Baatrup, E. (1985). Physiological studies on the pharyngeal terminal buds in the larval brook lamprey, *Lampetra planeri* (Bloch). *Chem. Senses* 10, 549–558. doi: 10.1093/chemse/10.4.549

Bandeira, F., Lent, R., and Herculano-Houzel, S. (2009). Changing numbers of neuronal and non-neuronal cells underlie postnatal brain growth in the rat. *Proc. Natl. Acad. Sci. U.S.A.* 106, 14108–14113. doi: 10.1073/pnas.0804650106

Barreiro-Iglesias, A., Anadon, R., and Rodicio, M. C. (2010). The gustatory system of lampreys. *Brain Behav. Evol.* 75, 241–250. doi: 10.1159/000315151

Barreiro-Iglesias, A., Villar-Cheda, B., Abalo, X.-M., Anadón, R., and Rodicio, M. C. (2008). The early scaffold of axon tracts in the brain of a primitive vertebrate, the sea lamprey. *Brain. Res. Bull.* 75, 42–52. doi: 10.1016/j.brainresbull.2007.07.020

Bartels, H., and Potter, I. C. (2004). Cellular composition and ultrastructure of the gill epithelium of larval and adult lampreys: implications for osmoregulation in fresh and seawater. *J. Exp. Biol.* 207, 3447–3462. doi: 10.1242/jeb.01157

Barton, K. (2014). *MuMIn: Multi-model Inference.* R Package Version 1.10.15. Available online at: http://CRAN.R-project.org/package=MuMIn

Barton, R. A., and Capellini, I. (2011). Maternal investment, life histories, and the costs of brain growth in mammals. *Proc. Natl. Acad. Sci. U.S.A.* 108, 6169–6174. doi: 10.1073/pnas.1019140108

Barton, R. A., and Harvey, P. H. (2000). Mosaic evolution of brain structure in mammals. *Nature* 405, 1055–1058. doi: 10.1038/35016580

Barton, R. A., Purvis, A., and Harvey, P. H. (1995). Evolutionary radiation of visual and olfactory brain systems in primates, bats and insectivores. *Philos. Trans. R. Soc. B* 348, 381–392. doi: 10.1098/rstb.1995.0076

Bauchot, R., Diagne, M., and Ribet, J. M. (1979). Post-hatching growth and allometry of the teleost brain. *J. Hirnforsch.* 20, 29–34.

Bethea, D. M., Buckel, J. A., and Carlson, J. K. (2004). Foraging ecology of the early life stages of four sympatric shark species. *Mar. Ecol. Prog. Ser.* 268, 245–264. doi: 10.3354/meps268245

Bhatnagar, K. P., Frahm, H. D., and Stephan, H. (1986). The pineal organ of bats: a comparative morphological and volumetric investigation. *J. Anat.* 147, 143–161.

Binder, T. R., and McDonald, D. G. (2007). Is there a role for vision in the behaviour of sea lampreys (*Petromyzon marinus*) during their upstream spawning migration? *Can. J. Fish. Aquat. Sci.* 64, 1403–1412. doi: 10.1139/f07-102

Binder, T. R., McDonald, D. G., and Wilkie, M. P. (2013). Reduced dermal photosensitivity in juvenile sea lampreys (*Petromyzon marinus*) reflects life-history-dependent changes in habitat and behaviour. *Can. J. Zool.* 91, 635–639. doi: 10.1139/cjz-2013-0041

Bodznick, D., and Northcutt, R. G. (1981). Electroreception in lampreys - evidence that the earliest vertebrates were electroreceptive. *Science* 212, 465–467. doi: 10.1126/science.7209544

Bowmaker, J. K., and Wagner, H.-J. (2004). Pineal organs of deep-sea fish: photopigments and structure. *J. Exp. Biol.* 207, 2379–2387. doi: 10.1242/jeb.01033

Boyd, J. L., Skove, S. L., Rouanet, J. P., Pilaz, L.-J., Bepler, T., Gordân, R., et al. (2015). Human-chimpanzee differences in a FZD8 enhancer alter cell-cycle dynamics in the developing neocortex. *Curr. Biol.* 25, 772–779. doi: 10.1016/j.cub.2015.01.041

Brandstätter, R., and Kotrschal, K. (1990). Brain growth patterns in 4 European cyprinid fish species (Cyprinidae, Teleostei): roach (*Rutilus rutilus*), bream (*Abramis brama*), common carp (*Cyprinus carpio*) and sabre carp (*Pelecus cultratus*). *Brain Behav. Evol.* 35, 195–211. doi: 10.1159/000115867

Butler, A. B., and Hodos, W. (1996). *Comparative Vertebrate Neuroanatomy: Evolution and Adaptation.* New York, NY: Wiley-Liss.

Calabrese, E., Badea, A., Watson, C., and Johnson, G. A. (2013). A quantitative magnetic resonance histology atlas of postnatal rat brain development with regional estimates of growth and variability. *Neuroimage* 71, 196–206. doi: 10.1016/j.neuroimage.2013.01.017

Candal, E., Anadon, R., Bourrat, F., and Rodriguez-Moldes, I. (2005). Cell proliferation in the developing and adult hindbrain and midbrain of trout and medaka (teleosts): a segmental approach. *Brain Res. Dev. Brain. Res.* 160, 157–175. doi: 10.1016/j.devbrainres.2005.08.009

Chang, M.-M., Wu, F., Miao, D., and Zhang, J. (2014). Discovery of fossil lamprey larva from the Lower Cretaceous reveals its three-phased life cycle. *Proc. Natl. Acad. Sci. U.S.A.* 111, 15486–15490. doi: 10.1073/pnas.1415716111

Chang, S., Chung-Davidson, Y. W., Libants, S. V., Nanlohy, K. G., Kiupel, M., Brown, C. T., et al. (2013). The sea lamprey has a primordial accessory olfactory system. *BMC Evol. Biol.* 13:172. doi: 10.1186/1471-2148-13-172

Charvet, C. J., Striedter, G. F., and Finlay, B. L. (2011). Evo-devo and brain scaling: candidate developmental mechanisms for variation and constancy in vertebrate brain evolution. *Brain Behav. Evol.* 78, 248–257. doi: 10.1159/000329851

Clark, D. A., Mitra, P. P., and Wang, S. S. (2001). Scalable architecture in mammalian brains. *Nature* 411, 189–193. doi: 10.1038/35075564

Cobley, N. D. (1996). An observation of live prey capture by black-browed albatross *Diomedea melanophrys*. *Mar. Ornithol.* 24, 45–46.

Cole, W. C., and Youson, J. H. (1981). The effect of pinealectomy, continuous light, and continuous darkness on metamorphosis of anadromous sea lampreys, *Petromyzon marinus* L. *J. Exp. Biol.* 218, 397–404. doi: 10.1002/jez.1402180311

Collin, S. P., Hart, N. S., Shand, J., and Potter, I. C. (2003). Morphology and spectral absorption characteristics of retinal photoreceptors in the southern hemisphere lamprey (*Geotria australis*). *Vis. Neurosci.* 20, 119–130. doi: 10.1017/S0952523803202030

Collin, S. P., Potter, I. C., and Braekevelt, C. R. (1999). The ocular morphology of the southern hemisphere lamprey *Geotria australis* gray, with special reference to optical specialisations and the characterisation and phylogeny of photoreceptor types. *Brain Behav. Evol.* 54, 96–118. doi: 10.1159/000006616

Cornide-Petronio, M. E., Barreiro-Iglesias, A., Anadon, R., and Rodicio, M. C. (2011). Retinotopy of visual projections to the optic tectum and pretectum in larval sea lamprey. *Exp. Eye Res.* 92, 274–281. doi: 10.1016/j.exer.2011.01.011

Currie, S. N., and Carlsen, R. C. (1988). Cranial components of startle behavior in larval and adult lampreys. *Neuroscience* 24, 709–718. doi: 10.1016/0306-4522(88)90363-6

Davies, W. L., Cowing, J. A., Carvalho, L. S., Potter, I. C., Trezise, A. E., Hunt, D. M., et al. (2007). Functional characterization, tuning, and regulation of visual pigment gene expression in an anadromous lamprey. *FASEB J.* 21, 2713–2724. doi: 10.1096/fj.06-8057com

Dawson, H. A., Quintella, B. R., Almeida, P. R., Treble, A. J., and Jolley, J. C. (2015). "The ecology of larval and metamorphosing lampreys," in *Lampreys: Biology, Conservation and Control,* ed M. F. Docker (New York, NY: Springer), 75–137.

Deacon, T. W. (1990). Problems of ontogeny and phylogeny in brain-size evolution. *Int. J. Primatol.* 11, 237–282. doi: 10.1007/BF02192870

De Arriba, M. D., and Pombal, M. A. (2007). Afferent connections of the optic tectum in lampreys: an experimental study. *Brain Behav. Evol.* 69, 37–68. doi: 10.1159/000095272

Deliagina, T. G., Ullen, F., Gonzalez, M. J., Efson, H. H., Orlovsky, G. N., and Grillner, S. (1995). Initiation of locomotion by lateral-line photoreceptors in lamprey - behavioral and neurophysiological studies. *J. Exp. Biol.* 198, 2581–2591.

De Miguel, E., and Anadon, R. (1987). The development of retina and the optic tectum of *Petromyzon marinus*, L. A light microscopic study. *J. Hirnforsch.* 28, 445–456.

De Miguel, E., Rodicio, C., and Anadon, R. (1990). Organization of the visual system in larval lampreys: an HRP study. *J. Comp. Neurol.* 302, 529–542. doi: 10.1002/cne.903020309

Derjean, D., Moussaddy, A., Atallah, E., St-Pierre, M., Auclair, F., Chang, S., et al. (2010). A novel neural substrate for the transformation of olfactory inputs into motor output. *PLoS Biol.* 8:e1000567. doi: 10.1371/journal.pbio.1000567

De Winter, W., and Oxnard, C. E. (2001). Evolutionary radiations and convergences in the structural organization of mammalian brains. *Nature* 409, 710–714. doi: 10.1038/35055547

Ebbesson, S. E. (1980). The parcellation theory and its relation to interspecific variability in brain organization, evolutionary and ontogenetic development, and neuronal plasticity. *Cell Tissue Res.* 213, 179–212. doi: 10.1007/BF00234781

Ebinger, P., Wächtler, K., and Stähler, S. (1983). Allometrical studies in the brain of cyclostomes. *J. Hirnforsch.* 24, 545–550.

Eddy, J. M. P. (1971). "The pineal complex," in *The Biology of Lampreys,* eds M. W. Hardisty and I. C. Potter (London: Academic Press), 91–103.

Eddy, J. M. P., and Strahan, R. (1968). The role of the pineal complex in the pigmentary effector system of the lampreys, *Mordacia mordax* (Richardson) and *Geotria australis* (Gray). *Gen. Comp. Endocrinol.* 11, 528–534. doi: 10.1016/0016-6480(68)90067-1

Eddy, J. M. P., and Strahan, R. (1970). The structure of the epiphyseal complex of *Mordacia mordax* and *Geotria australis* (Petromyzonidae). *Acta Zool.* 51, 67–84. doi: 10.1111/j.1463-6395.1970.tb00418.x

Ekström, P., and Meissl, H. (1997). The pineal organ of teleost fishes. *Rev. Fish. Biol. Fish.* 7, 199–284. doi: 10.1023/A:1018483627058

Ekström, P., and Meissl, H. (2003). Evolution of photosensory pineal organs in new light: the fate of neuroendocrine photoreceptors. *Philos. Trans. R. Soc. Lond. B* 358, 1679–1700. doi: 10.1098/rstb.2003.1303

Enequist, P. (1937). Das bachneunauge als ökologische modifikation des flussneunauges. Über die fluss – und bachneunaugen schwedens; vorläufige mitteilung. *Ark. Zool.* 29, 1–22.

Ericsson, J., Stephenson-Jones, M., Kardamakis, A., Robertson, B., Silberberg, G., and Grillner, S. (2013). Evolutionarily conserved differences in pallial and thalamic short-term synaptic plasticity in striatum. *J. Physiol.* 591, 859–874. doi: 10.1113/jphysiol.2012.236869

Finlay, B. L., and Darlington, R. B. (1995). Linked regularities in the development and evolution of mammalian brains. *Science* 268, 1578–1584. doi: 10.1126/science.7777856

Finlay, B. L., Darlington, R. B., and Nicastro, N. (2001). Developmental structure in brain evolution. *Behav. Brain Sciences* 24, 263–278. doi: 10.1017/S0140525X01003958

Freamat, M., and Sower, S. A. (2013). Integrative neuro-endocrine pathways in the control of reproduction in lamprey: a brief review. *Front. Endocrinol.* 4:151. doi: 10.3389/fendo.2013.00151

Fritzsch, B., and Northcutt, R. G. (1993a). Cranial and spinal nerve organization in amphioxus and lampreys: evidence for an ancestral craniate pattern. *Acta Anat.* 148, 96–109. doi: 10.1159/000147529

Fritzsch, B., and Northcutt, R. G. (1993b). Origin and migration of trochlear, oculomotor and abducent motor neurons in *Petromyzon marinus* L. *Brain Res. Dev. Brain Res.* 74, 122–126. doi: 10.1016/0165-3806(93)90091-N

Fu, Y., Rusznak, Z., Herculano-Houzel, S., Watson, C., and Paxinos, G. (2013). Cellular composition characterizing postnatal development and maturation of the mouse brain and spinal cord. *Brain Struct. Funct.* 218, 1337–1354. doi: 10.1007/s00429-012-0462-x

Gai, Z. K., Donoghue, P. C. J., Zhu, M., Janvier, P., and Stampanoni, M. (2011). Fossil jawless fish from China foreshadows early jawed vertebrate anatomy. *Nature* 476, 324–327. doi: 10.1038/nature10276

García-Fernández, J. M., and Foster, R. G. (1994). Immunocytochemical identification of photoreceptor proteins in hypothalamic cerebrospinal fluid-contacting neurons of the larval lamprey (*Petromyzon marinus*). *Cell Tissue Res.* 275, 319–326. doi: 10.1007/BF00319430

Gelman, S., Ayali, A., Kiemel, T., Sanovich, E., and Cohen, A. H. (2008). Metamorphosis-related changes in the lateral line system of lampreys, *Petromyzon marinus*. *J. Comp. Physiol. A.* 194, 945–956. doi: 10.1007/s00359-008-0367-6

Gelman, S., Ayali, A., Tytell, E. D., and Cohen, A. H. (2007). Larval lampreys possess a functional lateral line system. *J. Comp. Physiol. A* 193, 271–277. doi: 10.1007/s00359-006-0183-9

Gilland, E., and Baker, R. (2005). Evolutionary patterns of cranial nerve efferent nuclei in vertebrates. *Brain Behav. Evol.* 66, 234–254. doi: 10.1159/000088128

Gille, U., and Salomon, F. V. (2000). Brain growth in mallards, Pekin and Muscovy ducks (Anatidae). *J. Zool.* 252, 399–404. doi: 10.1111/j.1469-7998.2000.tb00635.x

Gonda, A., Herczeg, G., and Merila, J. (2011). Population variation in brain size of nine-spined sticklebacks (*Pungitius pungitius*)–local adaptation or environmentally induced variation? *BMC Evol. Biol.* 11:75. doi: 10.1186/1471-2148-11-75

Gonda, A., Herczeg, G., and Merilä, J. (2013). Evolutionary ecology of intraspecific brain size variation: a review. *Ecol. Evol.* 3, 2751–2764. doi: 10.1002/ece3.627

Gonzalez-Voyer, A., and Kolm, N. (2010). Sex, ecology and the brain: evolutionary correlates of brain structure volumes in *Tanganyikan cichlids*. *PLoS ONE* 5:e14355. doi: 10.1371/journal.pone.0014355

Gonzalez-Voyer, A., Winberg, S., and Kolm, N. (2009). Brain structure evolution in a basal vertebrate clade: evidence from phylogenetic comparative analysis of cichlid fishes. *BMC Evol. Biol.* 9:238. doi: 10.1186/1471-2148-9-238

Gould, S. J. (1975). Allometry in primates, with emphasis on scaling and the evolution of the brain. *Contrib. Primatol.* 5, 244–292.

Grillner, S., and Robertson, B. (2015). The basal ganglia downstream control of brainstem motor centres—an evolutionarily conserved strategy. *Curr. Opin. Neurobiol.* 33, 47–52. doi: 10.1016/j.conb.2015.01.019

Gritzenko, O. F. (1968). On the question of an ecological paralIelism between lampreys and salmon (in Russian). *Izv. Tikhookean. Nauchno-lssled. Inst. Rybn. Khoz. Okeanogr.* 65, 157–169.

Gruberg, E., Dudkin, E., Wang, Y., Marin, G., Salas, C., Sentis, E., et al. (2006). Influencing and interpreting visual input: the role of a visual feedback system. *J. Neurosci.* 26, 10368–10371. doi: 10.1523/JNEUROSCI.3288-06.2006

Guerin, A., D'aubenton-Carafa, Y., Marrakchi, E., Da Silva, C., Wincker, P., Mazan, S., et al. (2009). Neurodevelopment genes in lampreys reveal

trends for forebrain evolution in craniates. *PLoS ONE* 4:e5374. doi: 10.1371/journal.pone.0005374

Haldar, C., and Bishnupuri, K. S. (2001). Comparative view of pineal gland morphology of nocturnal and diurnal birds of tropical origin. *Microsc. Res. Tech.* 53, 25–32. doi: 10.1002/jemt.1065

Hardisty, M. W., and Potter, I. C. (1971). *The Biology of Lampreys.* London: Academic Press.

Healy, S. D., and Rowe, C. (2007). A critique of comparative studies of brain size. *Proc. R. Soc. Lond. B* 274, 453–464. doi: 10.1098/rspb.2006.3748

Heier, P. (1948). Fundamental principles in the structure of the brain of *Petromyzon fluviatilis*. *Acta Anat.* 5, 1–213.

Heimberg, A. M., Sempere, L. F., Moy, V. N., Donoghue, P. C. J., and Peterson, K. J. (2008). MicroRNAs and the advent of vertebrate morphological complexity. *Proc. Natl. Acad. Sci. U.S.A.* 105, 2946–2950. doi: 10.1073/pnas.0712259105

Herculano-Houzel, S. (2012). The remarkable, yet not extraordinary, human brain as a scaled-up primate brain and its associated cost. *Proc. Natl. Acad. Sci. U.S.A.* 109, 10661–10668. doi: 10.1073/pnas.1201895109

Heupel, M. R., and Simpfendorfer, C. A. (2011). Estuarine nursery areas provide a low-mortality environment for young bull sharks Carcharhinus leucas. *Mar. Ecol. Prog. Ser.* 433, 237–244. doi: 10.3354/meps09191

Hilliard, R. W., Bird, D. J., and Potter, I. C. (1983). Metamorphic changes in the intestine of three species of lampreys. *J. Morphol.* 176, 181–196. doi: 10.1002/jmor.1051760207

Hilliard, R. W., Potter, I. C., and Macey, D. J. (1985). The dentition and feeding mechanisms in adults of the Southern Hemisphere lamprey *Geotria australis* Gray. *Acta Zool.* 66, 159–170. doi: 10.1111/j.1463-6395.1985.tb00834.x

Homma, S. (1978). Organization of the trigeminal motor nucleus before and after metamorphosis in lampreys. *Brain Res.* 140, 33–42. doi: 10.1016/0006-8993(78)90236-6

Huber, R., van Staaden, M. J., Kaufman, L. S., and Liem, K. F. (1997). Microhabitat use, trophic patterns, and the evolution of brain structure in African cichlids. *Brain Behav. Evol.* 50, 167–182. doi: 10.1159/000113330

Hume, J. B., Adams, C. E., Mable, B., and Bean, C. W. (2013). Sneak male mating tactics between lampreys (*Petromyzontiformes*) exhibiting alternative life-history strategies. *J. Fish Biol.* 82, 1093–1100. doi: 10.1111/jfb.12047

Iribarne, L., and Castelló, M. E. (2014). Postnatal brain development of the pulse type, weakly electric gymnotid fish *Gymnotus omarorum*. *J. Physiol. Paris* 108, 47–60. doi: 10.1016/j.jphysparis.2014.05.001

Iwahori, N., Kawawaki, T., and Baba, J. (1999). Neuronal organization of the optic tectum in the river lamprey, *Lampetra japonica*: a Golgi study. *J. Hirnforsch.* 39, 409–424.

Iwaniuk, A. N., Gutierrez-Ibanez, C., Pakan, J. M., and Wylie, D. R. (2010). Allometric scaling of the tectofugal pathway in birds. *Brain Behav. Evol.* 75, 122–137. doi: 10.1159/000311729

Iwaniuk, A. N., and Hurd, P. L. (2005). The evolution of cerebrotypes in birds. *Brain Behav. Evol.* 65, 215–230. doi: 10.1159/000084313

Jacobs, L. F. (2012). From chemotaxis to the cognitive map: the function of olfaction. *Proc. Natl. Acad. Sci. U.S.A.* 109, 10693–10700. doi: 10.1073/pnas.1201880109

Janvier, P. (2008). Early jawless vertebrates and cyclostome origins. *Zoolog. Sci.* 25, 1045–1056. doi: 10.2108/zsj.25.1045

Jellyman, D. J., Glova, G. J., and Sykes, J. R. E. (2002). Movements and habitats of adult lamprey (*Geotria australis)* in two New Zealand waterways. *N. Z. J. Mar. Freshwatwer. Res.* 36, 53–65. doi: 10.1080/00288330.2002.9517070

Jerison, H. J. (1977). The theory of encephalization. *Ann. N. Y. Acad. Sci.* 299, 146–160. doi: 10.1111/j.1749-6632.1977.tb41903.x

Johnson, N. S., Buchinger, T. J., and Li, W. (2015). "Reproductive ecology of lampreys," in *Lampreys: Biology, Conservation and Control,* ed M. F. Docker (New York, NY: Springer), 265–303.

Johnson, N. S., Siefkes, M. J., and Li, W. (2005). Capture of ovulating female sea lampreys in traps baited with spermiating male sea lampreys. *North Am. J. Fish. Manage.* 25, 67–72. doi: 10.1577/M03-226.1

Johnson, N. S., Yun, S. S., Thompson, H. T., Brant, C. O., and Li, W. (2009). A synthesized pheromone induces upstream movement in female sea lamprey and summons them into traps. *Proc. Natl. Acad. Sci. U.S.A.* 106, 1021–1026. doi: 10.1073/pnas.0808530106

Johnston, J. B. (1902). The brain of Petromyzon. *J. Comp. Neurol.* 12, 1–86. doi: 10.1002/cne.910120102

Johnston, J. B. (1912). The telencephalon in cyclostomes. *J. Comp. Neurol.* 22, 341–404. doi: 10.1002/cne.900220401

Jones, M. R., Grillner, S., and Robertson, B. (2009). Selective projection patterns from subtypes of retinal ganglion cells to tectum and pretectum: distribution and relation to behavior. *J. Comp. Neurol.* 517, 257–275. doi: 10.1002/cne.22154

Jørgensen, J. (2005). "Morphology of electroreceptive sensory organs," in *Electroreception*, eds T. Bullock, C. Hopkins, A. Popper and R. Fay (New York, NY: Springer), 47–67.

Karamian, A. I., Vesselkin, N. P., Belekhova, M. G., and Zagorulko, T. M. (1966). Electrophysiological characteristics of tectal and thalamo-cortical divisions of the visual system in lower vertebrates. *J. Comp. Neurol.* 127, 559–576. doi: 10.1002/cne.901270408

Karamian, A. I., Vesselkin, N. P., and Agayan, A. L. (1984). "Electrophysiological and behavioral studies of the optic tectum in cyclostomes," in *Comparative Neurology of the Optic Tectum*, ed H. Vanegas (New York, NY: Plenum Press), 15–30.

Kardamakis, A. A., Saitoh, K., and Grillner, S. (2015). Tectal microcircuit generating visual selection commands on gaze-controlling neurons. *Proc. Natl. Acad. Sci. U.S.A.* 112, E1956–E1965. doi: 10.1073/pnas.1504866112

Kaslin, J., Ganz, J., and Brand, M. (2008). Proliferation, neurogenesis and regeneration in the non-mammalian vertebrate brain. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 363, 101–122. doi: 10.1098/rstb.2006.2015

Kempermann, G. (2012). New neurons for 'survival of the fittest.' *Nat. Rev. Neurosci.* 13, 727–736. doi: 10.1038/nrn3319

Kennedy, M. C., and Rubinson, K. (1977). Retinal projections in larval, transforming and adult sea lamprey, *Petromyzon marinus*. *J. Comp. Neurol.* 171, 465–479. doi: 10.1002/cne.901710404

Khonsari, R. H., Li, B., Vernier, P., Northcutt, R. G., and Janvier, P. (2009). Agnathan brain anatomy and craniate phylogeny. *Acta Zool.* 90, 52–68. doi: 10.1111/j.1463-6395.2008.00388.x

Kingsford, M. J., Leis, J. M., Shanks, A., Lindeman, K. C., Morgan, S. G., and Pineda, J. (2002). Sensory environments, larval abilities and local self-recruitment. *Bull. Mar. Sci.* 70, 309–340.

Kolm, N., Gonzalez-Voyer, A., Brelin, D., and Winberg, S. (2009). Evidence for small scale variation in the vertebrate brain: mating strategy and sex affect brain size and structure in wild brown trout (*Salmo trutta*). *J. Evol. Biol.* 22, 2524–2531. doi: 10.1111/j.1420-9101.2009.01875.x

Kosareva, A. A. (1980). Retinal projections in lamprey (*Lampetra fluviatilis*). *J. Hirnforsch.* 21, 243–256.

Kotrschal, A., Heckel, G., Bonfils, D., and Taborsky, B. (2012). Life-stage specific environments in a cichlid fish: implications for inducible maternal effects. *Evol. Ecol.* 26, 123–137. doi: 10.1007/s10682-011-9495-5

Kotrschal, K., Adam, H., Brandstätter, R., Junger, H., Zaunreiter, M., and Goldschmid, A. (1990). Larval size constraints determine directional ontogenetic shifts in the visual system of teleosts. *J. Zoolog. Syst. Evol. Res.* 28, 166–182. doi: 10.1111/j.1439-0469.1990.tb00374.x

Kotrschal, K., and Palzenberger, M. (1992). Neuroecology of cyprinids: comparative, quantitative histology reveals diverse brain patterns. *Environ. Biol. Fish.* 33, 135–152. doi: 10.1007/BF00002560

Kruska, D. C. T. (1988). The brain of the basking shark (*Cetorhinus maximus)*. *Brain Behav. Evol.* 32, 353–363. doi: 10.1159/000116562

Kruska, D. C. T. (2005). On the evolutionary significance of encephalization in some eutherian mammals: effects of adaptive radiation, domestication, and feralization. *Brain Behav. Evol.* 65, 73–108. doi: 10.1159/000082979

Kumar, S., and Hedges, S. B. (1998). A molecular timescale for vertebrate evolution. *Nature* 392, 917–920. doi: 10.1038/31927

Kuratani, S., Ueki, T., Aizawa, S., and Hirano, S. (1997). Peripheral development of cranial nerves in a cyclostome, *Lampetra japonica*: morphological distribution of nerve branches and the vertebrate body plan. *J. Comp. Neurol.* 384, 483–500.

Lecchini, D., Lecellier, G., Lanyon, R. G., Holles, S., Poucet, B., and Duran, E. (2014). Variation in brain organization of coral reef fish larvae according to life history traits. *Brain Behav. Evol.* 83, 17–30. doi: 10.1159/000356787

Lefebvre, L., Reader, S. M., and Sol, D. (2004). Brains, innovations and evolution in birds and primates. *Brain Behav. Evol.* 63, 233–246. doi: 10.1159/000076784

Lethbridge, R. C., and Potter, I. C. (1981). The development of teeth and associated feeding structures during the metamorphosis of the lamprey, *Geotria australis*. *Acta Zool.* 62, 201–214. doi: 10.1111/j.1463-6395.1981.tb00629.x

Leyhausen, C., Kirschbaum, F., Szabo, T., and Erdelen, M. (1987). Differential growth in the brain of the weakly electric fish, *Apteronotus leptorhynchus* (Gymnotiformes), during ontogeny. *Brain Behav. Evol.* 30, 230–248. doi: 10.1159/000118648

Lisney, T. J., Bennett, M. B., and Collin, S. P. (2007). Volumetric analysis of the sensory brain areas indicates ontogenetic shifts in the relative importance of sensory systems in elasmobranchs. *Raff. Bull. Zool.* 14, 7–15. doi: 10.1111/j.0022-1112.2006.00940.x

Lisney, T. J., and Collin, S. P. (2006). Brain morphology in large pelagic fishes: a comparison between sharks and teleosts. *J. Fish Biol.* 68, 532–554. doi: 10.1111/j.0022-1112.2006.00940.x

Manzon, R. G., Youson, J. H., and Holmes, J. A. (2015). "Lamprey metamorphosis," in *Lampreys: Biology, Conservation and Control,* ed M. F. Docker (New York, NY: Springer), 139–214.

McMenamin, S. K., and Parichy, D. M. (2013). Metamorphosis in teleosts. *Curr. Top. Dev. Biol.* 103, 127–165. doi: 10.1016/b978-0-12-385979-2.00005-8

Melendez-Ferro, M., Perez-Costas, E., Villar-Cheda, B., Rodriguez-Munoz, R., Anadon, R., and Rodicio, M. C. (2003). Ontogeny of gamma-aminobutyric acid-immunoreactive neurons in the rhombencephalon and spinal cord of the sea lamprey. *J. Comp. Neurol.* 464, 17–35. doi: 10.1002/cne.10773

Melendez-Ferro, M., Villar-Cheda, B., Abalo, X. M., Perez-Costas, E., Rodriguez-Munoz, R., Degrip, W. J., et al. (2002). Early development of the retina and pineal complex in the sea lamprey: comparative immunocytochemical study. *J. Comp. Neurol.* 442, 250–265. doi: 10.1002/cne.10090

Meyer-Rochow, V. B., and Stewart, D. (1996). Review of larval and postlarval eye ultrastructure in the lamprey (Cyclostomata) with special emphasis on *Geotria australis* (Gray). *Microsc. Res. Tech.* 35, 431–444.

Montgomery, J. C., Bodznick, D., and Yopak, K. E. (2012). The cerebellum and cerebellum-like structures of cartilaginous fishes. *Brain Behav. Evol.* 80, 152–165. doi: 10.1159/000339868

Montgomery, J. C., and Sutherland, K. B. W. (1997). Sensory development of the antarctic silverfish *Pleuragramma antarcticum*: a test for the ontogenetic shift hypothesis. *Polar Biol.* 18, 112–115. doi: 10.1007/s003000050165

Moore, J. W., and Mallat, J. M. (1980). Feeding of larval lamprey. *Can. J. Fish. Aquat. Sci.* 37, 1658–1664. doi: 10.1139/f80-213

Neira, F. J. (1984). Biomorfología de las lampreas parasitarias chilenas *Geotria australis* (Gray, 1851) y *Mordacia lapicida* (Gray, 1851)(Petromyzontiformes). *Gayana Zool.* 48, 3–40.

Ngwenya, A., Patzke, N., Spocter, M. A., Kruger, J.-L., Dell, L.-A., Chawana, R., et al. (2013). The continuously growing central nervous system of the Nile crocodile (*Crocodylus niloticus*). *Anat. Rec.* 296, 1489–1500. doi: 10.1002/ar.22752

Nieuwenhuys, R. (1977). The brain of the lamprey in a comparative perspective. *Ann. N. Y. Acad. Sci.* 299, 97–145. doi: 10.1111/j.1749-6632.1977.tb41902.x

Nieuwenhuys, R., and Nicholson, C. (1998). "Lampreys, Petromyzontoidae," in *The Central Nervous System of Vertebrates*, eds R. Nieuwenhuys, H. J. T. Donkelaar, and C. Nicholson (Berlin: Springer), 397–495. doi: 10.1007/978-3-642-18262-4_10

Northcutt, R. G. (2002). Understanding vertebrate brain evolution. *Integr. Comp. Biol.* 42, 743–756. doi: 10.1093/icb/42.4.743

Northcutt, R. G., and Puzdrowski, R. L. (1988). Projections of the olfactory bulb and nervus terminalis in the silver lamprey. *Brain Behav. Evol.* 32, 96–107. doi: 10.1159/000116537

Northcutt, R. G., and Wicht, H. (1997). Afferent and efferent connections of the lateral and medial pallia of the silver lamprey. *Brain Behav. Evol.* 49, 1–19. doi: 10.1159/000112978

Ocaña, F. M., Suryanarayana, S. M., Saitoh, K., Kardamakis, A. A., Capantini, L., Robertson, B., et al. (2015). The lamprey pallium provides a blueprint of the mammalian motor projections from cortex. *Curr. Biol.* 25, 413–423. doi: 10.1016/j.cub.2014.12.013

Ota, K. G., and Kuratani, S. (2007). Cyclostome embryology and early evolutionary history of vertebrates. *Integr. Comp. Biol.* 47, 329–337. doi: 10.1093/icb/icm022

Paton, K. R., Cake, M. H., and Potter, I. C. (2011). Metabolic responses to exhaustive exercise change markedly during the protracted non-trophic spawning migration of the lamprey *Geotria australis*. *J. Comp. Physiol. B* 181, 751–763. doi: 10.1007/s00360-011-0570-6

Pena, E. A., and Slate, E. H. (2014). *gvlma: Global Validation of Linear Models Assumptions*. R Package Version 1.0.0.2. Available online at: http://CRAN.R-project.org/package=gvlma

Piavis, G. W. (1971). "Embriology," in *The Biology of Lampreys*, eds M. W. Hardisty and I. C. Potter (London: Academic Press), 361–400.

Pirlot, P., and Bernier, R. (1991). Brain growth and differentiation in two fetal bats: qualitative and quantitative aspects. *Am. J. Anat.* 190, 167–181. doi: 10.1002/aja.1001900206

Platel, R., and Delfini, C. (1981). L'Encéphalisation chez la myxine (*Myxine glutinosa* L.). Analyse quantifiée des principales subdivisions encéphaliques. *Cah. Biol. Mar.* 22, 407–430.

Platel, R., and Delfini, C. (1986). L'Encéphalisation chez la lamproie marine, *Petromyzon marinus* (L.). Analyse quantifiée des principales subdivisions encéphaliques. *J. Hirnforsch.* 3, 279–293.

Platel, R., and Vesselkin, N. P. (1988). Analysis of brain-body allometries in the lamprey *Lampetra fluviatilis* L. *J. Evol. Biochem. Phys.* 24, 138–145.

Platel, R., and Vesselkin, N. P. (1989). Comparative study of the encephalization in 3 species of Petromyzonidae (agnatha) - *Petromyzon marinus*, *Lampetra fluviatilis* and *Lampetra planeri*. *J. Hirnforsch.* 30, 23–32.

Polenova, O. A., and Vesselkin, N. P. (1993). Olfactory and nonolfactory projections in the river lamprey (*Lampetra fluviatilis*) telencephalon. *J. Hirnforsch.* 34, 261–279.

Pollen, A. A., Dobberfuhl, A. P., Scace, J., Igulu, M. M., Renn, S. C. P., Shumway, C. A., et al. (2007). Environmental complexity and social organization sculpt the brain in Lake Tanganyikan cichlid fish. *Brain. Behav. Evol.* 70, 21–39. doi: 10.1159/000101067

Pombal, M. A., Alvarez-Otero, R., Perez-Fernandez, J., Solveira, C., and Megias, M. (2011). Development and organization of the lamprey telencephalon with special reference to the GABAergic system. *Front. Neuroanat.* 5:20. doi: 10.3389/fnana.2011.00020

Pombal, M. A., Marin, O., and Gonzalez, A. (2001). Distribution of choline acetyltransferase-immunoreactive structures in the lamprey brain. *J. Comp. Neurol.* 431, 105–126. doi: 10.1002/1096-9861(20010226)431:13.0.CO;2-P

Pombal, M. A., Megias, M., Bardet, S. M., and Puelles, L. (2009). New and old thoughts on the segmental organization of the forebrain in lampreys. *Brain Behav. Evol.* 74, 7–19. doi: 10.1159/000229009

Pombal, M. A., and Puelles, L. (1999). Prosomeric map of the lamprey forebrain based on calretinin immunocytochemistry, Nissl stain, and ancillary markers. *J. Comp. Neurol.* 414, 391–422.

Pombal, M. A., Rodicio, M. C., and Anadon, R. (1994). Development and organization of the ocular motor nuclei in the larval sea lamprey, *Petromyzon marinus* L.: an HRP study. *J. Comp. Neurol.* 341, 393–406. doi: 10.1002/cne.903410309

Pombal, M. A., Yanez, J., Marin, O., Gonzalez, A., and Anadon, R. (1999). Cholinergic and GABAergic neuronal elements in the pineal organ of lampreys, and tract-tracing observations of differential connections of pinealofugal neurons. *Cell Tissue Res.* 295, 215–223. doi: 10.1007/s004410051227

Potter, I. C. (1980). Ecology of larval and metamorphosing lampreys. *Can. J. Fish. Aquat. Sci.* 37, 1641–1657. doi: 10.1139/f80-212

Potter, I. C., Gill, H. S., Renaud, C. B., and Haoucher, D. (2015). "The taxonomy, phylogeny, and distribution of lampreys," in *Lampreys: Biology, Conservation and Control,* ed M. F. Docker (New York, NY: Springer), 35–73.

Potter, I. C., and Hilliard, R. W. (1986). Growth and the average duration of larval life in the southern hemisphere lamprey, *Geotria australis* Gray. *Experientia* 42, 1170–1173. doi: 10.1007/BF01941297

Potter, I. C., Hilliard, R. W., and Bird, D. J. (1980). Metamorphosis in the southern hemisphere lamprey, *Geotria australis*. *J. Zool.* 190, 405–430. doi: 10.1111/j.1469-7998.1980.tb01435.x

Potter, I. C., Hilliard, R. W., Bird, D. J., and Macey, D. J. (1983). Quantitative data on morphology and organ weights during the protracted spawning−run period of the Southern Hemisphere lamprey *Geotria australis*. *J. Zool.* 200, 1–20. doi: 10.1111/j.1469-7998.1983.tb06106.x

Potter, I. C., Prince, P. A., and Croxall, J. P. (1979). Data on the adult marine and migratory phases in the life cycle of the southern hemisphere lamprey, *Geotria australis* Gray. *Env. Biol. Fishes* 4, 65–69. doi: 10.1007/BF00005929

Puzdrowski, R. L., and Northcutt, R. G. (1989). Central projections of the pineal complex in the silver lamprey *Ichthyomyzon unicuspis*. *Cell Tissue Res.* 255, 269–274. doi: 10.1007/BF00224108

Ralph, C. L. (1975). The pineal gland and geographical distribution of animals. *Int. J. Biometeorol.* 19, 289–303. doi: 10.1007/BF01451040

Rasband, W. S. (1997). *ImageJ*. Bethesda, MD: U. S. National Institutes of Health. 1997–2014. Available online at: http://imagej.nih.gov/ij/

R Core Team. (2013). *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing.

Reep, R. L., Finlay, B. L., and Darlington, R. B. (2007). The limbic system in mammalian brain evolution. *Brain Behav. Evol.* 70, 57–70. doi: 10.1159/000101491

Reis-Santos, P., McCormick, S. D., and Wilson, J. M. (2008). Ionoregulatory changes during metamorphosis and salinity exposure of juvenile sea lamprey (*Petromyzon marinus* L.). *J. Exp. Biol.* 211, 978–988. doi: 10.1242/jeb.014423

Ren, X., Chang, S., Laframboise, A., Green, W., Dubuc, R., and Zielinski, B. (2009). Projections from the accessory olfactory organ into the medial region of the olfactory bulb in the sea lamprey (*Petromyzon marinus*): a novel vertebrate sensory structure? *J. Comp. Neurol.* 516, 105–116. doi: 10.1002/cne.22100

Renaud, C. B. (2011). *Lampreys of the World - An Annotated and Illustrated Catalogue of Lamprey Species Known to Date*. Rome: Food and Agriculture Organization of the United Nations (FAO).

Renaud, C. B., Gill, H. S., and Potter, I. C. (2009). Relationships between the diets and characteristics of the dentition, buccal glands and velar tentacles of the adults of the parasitic species of lamprey. *J. Zool.* 278, 231–242. doi: 10.1111/j.1469-7998.2009.00571.x

Richardson, M. K., Admiraal, J., and Wright, G. M. (2010). Developmental anatomy of lampreys. *Biol. Rev.* 85, 1–33. doi: 10.1111/j.1469-185X.2009.00092.x

Robertson, B., Saitoh, K., Menard, A., and Grillner, S. (2006). Afferents of the lamprey optic tectum with special reference to the GABA input: combined tracing and immunohistochemical study. *J. Comp. Neurol.* 499, 106–119. doi: 10.1002/cne.21078

Ronan, M. (1988). Anatomical and physiological evidence for electroreception in larval lampreys. *Brain Res.* 448, 173–177. doi: 10.1016/0006-8993(88)91115-8

Ronan, M., and Bodznick, D. (1991). Behavioral and neurophysiological demonstration of a lateralis skin photosensitivity in larval sea lampreys. *J. Exp. Biol.* 161, 97–117.

Ronan, M., and Northcutt, R. G. (1990). Projections ascending from the spinal cord to the brain in petromyzontid and myxinoid agnathans. *J. Comp. Neurol.* 291, 491–508. doi: 10.1002/cne.902910402

Rovainen, C. M. (1979). Neurobiology of lampreys. *Physiol. Rev.* 59, 1007–1077.

Rovainen, C. M. (1996). Feeding and breathing in lampreys. *Brain Behav. Evol.* 48, 297–305. doi: 10.1159/000113208

Rubinson, K. (1990). The developing visual system and metamorphosis in the lamprey. *J. Neurobiol.* 21, 1123–1135. doi: 10.1002/neu.480210715

Saitoh, K., Menard, A., and Grillner, S. (2007). Tectal control of locomotion, steering, and eye movements in lamprey. *J. Neurophysiol.* 97, 3093–3108. doi: 10.1152/jn.00639.2006

Sala, R., Santamaría, C. A., and Crespo, S. (2005). Growth of organ systems of *Dentex dentex* (L) and *Psetta maxima* (L) during larval development. *J. Fish Biol.* 66, 315–326. doi: 10.1111/j.0022-1112.2005.00580.x

Scott, W. B. (1887). Notes on the development of Petromyzon. *J. Morphol.* 1, 253–310. doi: 10.1002/jmor.1050010203

Siefkes, M. J., Scott, A. P., Zielinski, B., Yun, S. S., and Li, W. (2003). Male sea lampreys, *Petromyzon marinus* L., excrete a sex pheromone from gill epithelia. *Biol. Reprod.* 69, 125–132. doi: 10.1095/biolreprod.102.014472

Smith, J. J., Kuraku, S., Holt, C., Sauka-Spengler, T., Jiang, N., Campbell, M. S., et al. (2013). Sequencing of the sea lamprey (*Petromyzon marinus*) genome provides insights into vertebrate evolution. *Nat. Genet.* 45, 415–421. doi: 10.1038/ng.2568

Sorensen, P. W., Fine, J. M., Dvornikovs, V., Jeffrey, C. S., Shao, F., Wang, J., et al. (2005). Mixture of new sulfated steroids functions as a migratory pheromone in the sea lamprey. *Nat. Chem. Biol.* 1, 324–328. doi: 10.1038/nchembio739

Sousa, R., Araújo, M. J., and Antunes, C. (2012). Habitat modifications by sea lampreys (Petromyzon marinus) during the spawning season: effects on sediments. *J. Appl. Ichthyol.* 28, 766–771. doi: 10.1111/j.1439-0426.2012.02025.x

Stephan, H. (1960). Methodische studien über den quantitativen vergleich architektonischer struktureinheiten des gehirns. *Z. Wiss. Zool.* 64, 143–172.

Striedter, G. F. (2005). *Principles of Brain Evolution*. Sunderland, MA: Sinauer Associates, Inc.

Suárez, R., Garcia-Gonzalez, D., and De Castro, F. (2012). Mutual influences between the main olfactory and vomeronasal systems in development and evolution. *Front. Neuroanat.* 6:50. doi: 10.3389/fnana.2012.00050

Suárez, R., Gobius, I., and Richards, L. J. (2014). Evolution and development of interhemispheric connections in the vertebrate forebrain. *Front. Hum. Neurosci.* 8:497. doi: 10.3389/fnhum.2014.00497

Tamotsu, S., and Morita, Y. (1986). Photoreception in pineal organs of larval and adult lampreys, *Lampetra japonica*. *J. Comp. Physiol.* 159, 1–5. doi: 10.1007/BF00612489

Tomoda, H., and Uematsu, K. (1996). Morphogenesis of the brain in larval and juvenile Japanese eels, *Anguilla japonica*. *Brain Behav. Evol.* 47, 33–41. doi: 10.1159/000113227

Ullen, F., Deliagina, T. G., Orlovsky, G. N., and Grillner, S. (1995). Spatial orientation in the lamprey. 2. Visual influence on orientation during locomotion and in the attached state. *J. Exp. Biol.* 198, 675–681.

Ullen, F., Deliagina, T. G., Orlovsky, G. N., and Grillner, S. (1997). Visual pathways for postural control and negative phototaxis in lamprey. *J. Neurophysiol.* 78, 960–976.

Vandenbossche, J., Seelye, J. G., and Zielinski, B. S. (1995). The morphology of the olfactory epithelium in larval, juvenile and upstream migrant stages of the sea lamprey, *Petromyzon marinus*. *Brain Behav. Evol.* 45, 19–24. doi: 10.1159/000113382

Vernadakis, A. J., Bemis, W. E., and Bittman, E. L. (1998). Localization and partial characterization of melatonin receptors in amphioxus, hagfish, lamprey, and skate. *Gen. Comp. Endocr.* 110, 67–78. doi: 10.1006/gcen.1997.7042

Vidal Pizarro, I., Swain, G. P., and Selzer, M. E. (2004). Cell proliferation in the lamprey central nervous system. *J. Comp. Neurol.* 469, 298–310. doi: 10.1002/cne.11013

Vigh, B., Manzano, M. J., Zadori, A., Frank, C. L., Lukats, A., Rohlich, P., et al. (2002). Nonvisual photoreceptors of the deep brain, pineal organs and retina. *Histol. Histopathol.* 17, 555–590.

Villar-Cheda, B., Abalo, X. M., Villar-Cervino, V., Barreiro-Iglesias, A., Anadon, R., and Rodicio, M. C. (2008). Late proliferation and photoreceptor differentiation in the transforming lamprey retina. *Brain Res.* 1201, 60–67. doi: 10.1016/j.brainres.2008.01.077

Villar-Cheda, B., Perez-Costas, E., Melendez-Ferro, M., Abalo, X. M., Rodriguez-Munoz, R., Anadon, R., et al. (2006). Cell proliferation in the forebrain and midbrain of the sea lamprey. *J. Comp. Neurol.* 494, 986–1006. doi: 10.1002/cne.20851

Vrieze, L. A., Bergstedt, R. A., and Sorensen, P. W. (2011). Olfactory-mediated stream-finding behavior of migratory adult sea lamprey (*Petromyzon marinus*). *Can. J. Fish. Aquat. Sci.* 68, 523–533. doi: 10.1139/F10-169

Vrieze, L. A., Bjerselius, R., and Sorensen, P. W. (2010). Importance of the olfactory sense to migratory sea lampreys *Petromyzon marinus* seeking riverine spawning habitat. *J. Fish Biol.* 76, 949–964. doi: 10.1111/j.1095-8649.2010.02548.x

Vrieze, L. A., and Sorensen, P. W. (2001). Laboratory assessment of the role of a larval pheromone and natural stream odor in spawning stream localization by migratory sea lamprey (*Petromyzon marinus*). *Can. J. Fish. Aquat. Sci.* 58, 2374–2385. doi: 10.1139/f01-179

Wagner, C. M., Twohey, M. B., and Fine, J. M. (2009). Conspecific cueing in the sea lamprey: do reproductive migrations consistently follow the most intense larval odour? *Anim. Behav.* 78, 593–599. doi: 10.1016/j.anbehav.2009.04.027

Wagner, H. J. (2001). Sensory brain areas in mesopelagic fishes. *Brain Behav. Evol.* 57, 117–133. doi: 10.1159/000047231

Wagner, H. J. (2003). Volumetric analysis of brain areas indicates a shift in sensory orientation during development in the deep-sea grenadier *Coryphaenoides armatus*. *Mar. Biol.* 142, 791–797. doi: 10.1007/s00227-002-0990-7

Wagner, H. J., and Mattheus, U. (2002). Pineal organs in deep demersal fish. *Cell Tissue Res.* 307, 115–127. doi: 10.1007/s00441-001-0482-y

Weigle, C., and Northcutt, R. G. (1998). To the phylogenetic origin of the cerebellum: tracing studies on the silver lamprey *Ichthyomyzon unicuspis*. *Eur. J. Neurosci.* 10, 196–196.

Weigle, C., and Northcutt, R. G. (1999). The chemoarchitecture of the forebrain of lampreys: evolutionary implications by comparisons with gnathostomes. *Eur. J. Morphol.* 37, 122–125. doi: 10.1076/ejom.37.2-3.0122

Wicht, H. (1996). The brains of lampreys and hagfishes: characteristics, characters, and comparisons. *Brain Behav. Evol.* 48, 248–261. doi: 10.1159/000113204

Willemet, R. (2012). Understanding the evolution of mammalian brain structures; the need for a (new) cerebrotype approach. *Brain Sci.* 2, 203–224. doi: 10.3390/brainsci2020203

Willemet, R. (2013). Reconsidering the evolution of brain, cognition, and behavior in birds and mammals. *Front. Psychol.* 4:396. doi: 10.3389/fpsyg.2013.00396

Yáñez, J., Pombal, M. A., and Anadón, R. (1999). Afferent and efferent connections of the parapineal organ in lampreys: a tract tracing and immunocytochemical study. *J. Comp. Neurol.* 403, 171–189.

Yopak, K. E. (2012). Neuroecology of cartilaginous fishes: the functional implications of brain scaling. *J. Fish Biol.* 80, 1968–2023. doi: 10.1111/j.1095-8649.2012.03254.x

Yopak, K. E., and Frank, L. R. (2009). Brain size and brain organization of the whale shark, *Rhincodon typus*, using magnetic resonance imaging. *Brain Behav. Evol.* 74, 121–142. doi: 10.1159/000235962

Yopak, K. E., and Lisney, T. J. (2012). Allometric scaling of the optic tectum in cartilaginous fishes. *Brain Behav. Evol.* 80, 108–126. doi: 10.1159/000339875

Yopak, K. E., Lisney, T. J., Darlington, R. B., Collin, S. P., Montgomery, J. C., and Finlay, B. L. (2010). A conserved pattern of brain scaling from sharks to primates. *Proc. Natl. Acad. Sci. U.S.A.* 107, 12946–12951. doi: 10.1073/pnas.1002195107

Yopak, K. E., and Montgomery, J. C. (2008). Brain organization and specialization in deep-sea chondrichthyans. *Brain Behav. Evol.* 71, 287–304. doi: 10.1159/000127048

Yopak, K. E., Lisney, T. J., and Collin, S. P. (2015). Not all sharks are "swimming noses": variation in olfactory bulb size in cartilaginous fishes. *Brain Struct. Funct.* 220, 1127–1143. doi: 10.1007/s00429-014-0705-0

Youson, J. H., Wright, G. M., and Ooi, E. C. (1977). The timing of changes in several internal organs during metamorphosis of anadromous larval lamprey *Petromyzon marinus*. *Can. J. Zool.* 55, 469–473. doi: 10.1139/z77-063

Zielinski, B., Fredricks, K., McDonald, R., and Zaidi, A. (2005). Morphological and electrophysiological examination of olfactory sensory neurons during the early developmental prolarval stage of the sea lamprey *Petromyzon marinus* L. *J. Neurocytol.* 34, 209–216. doi: 10.1007/s11068-005-8354-0

Conflict of Interest Statement: The Reviewer Thomas Lisney declares that, despite being affiliated to the same institution as authors Carlos A. Salas, Kara E. Yopak, Rachael E. Warrington, Nathan S. Hart and Shaun P. Collin, the review process was handled objectively and no conflict of interest exists. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership