Cranial nerves are relevant because all that everyone smells, sees, feels in the face, says, hears, senses equilibrium, moves the head, swallows, breathes, and heart beats, is led and mediated by cranial nerves. Cranial nerves carry the information from sensory organs to the brain, and the instructions for the muscles of all these organs in the face, neck, heart, and abdomen. While I was working at the Institute of Psychiatry at King's College in London in 2002, one of my best friends suffered a traffic accident while riding on his motorcycle, without a helmet. This accident increased my panic and care to everything that could lead to an accident, and made the “Mind the Gap” warnings in the London tube more obvious to me than ever. My friend was enjoying a fantastic plan that wonderful June Sunday morning, consisting of riding a motorcycle through the beautiful mountains close to Madrid and finish back to the city to drink vermouth. After the accident, he became anosmic. Several weeks later, I learned that my friend had broken the base of the skull and the lamina cribosa, affecting the first cranial nerve, the olfactory nerve. He never recovered the sense of smell because he did not care enough about his head. My lesson was mind the head. In spite of being so relevant for injury treatment and surgery repair or nerve regeneration, much is still unknown about cranial nerve function, development, evolution, and morphology. One of the most obvious reasons is because of high complexity of the cranial nerves, in turn explaining the extreme interspecific heterogeneity, and intraspecific variability. This variability, for example, directly leads to an extreme difficulty in regenerative therapy approaches and reconstructive surgery in humans. What do we know about the reasons why the cranial nerves show this organizational and functional profile?

To answer this question, this Special Issue of The Anatomical Record revises and updates the most recent knowledge and points of view about a number of topics related to cranial nerves. The co-Guest Editors responsible for the organization, recruitment, and compilation of the papers are Alino Martínez-Marcos and José Ramón Sañudo. Prof. Martínez-Marcos is Dean of the School of Medicine at University of Castilla-LaMancha, and has focused his investigations on the comparative neuroanatomy of some sensory and motor systems in a number of different taxa, olfactory, and vromeronasal systems in snakes, opossums, and rodents, and neural basis of tongue-flicking behavior from the vromeronasal system to the hypoglossal nerve. At present, he is involved in investigating the involvement of the olfactory and vagal systems in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Prof. Sañudo is Full Professor and Head of the Department of Anatomy and Embryology of the University Complutense of Madrid (Spain). He has investigated in Clinical Anatomy and Embryology the last 40 years, publishing over 80 papers related to the facial and vagal cranial nerves. Both colleagues have done a remarkable, impressive work compiling 23 cutting-edge pieces of knowledge around cranial nerves, recruiting some of the known experts in the field. These articles belong to two groups, according to the key aspects of cranial nerve investigation: Ontogeny/Phylogeny and Morphology/ Clinical Significance. The articles in the first group (Volume 1 of this Special Issue) raise relevant questions on cranial nerve patterning and comparative anatomy (with one of its interesting focus on amphioxus and lampreys), and provide new insights into the mechanisms underlying the development of the eye, and the oculomotor and vestibular complexes. The articles in the second group (Volume 2 of this Special Issue) explore the features of the extra- and intra-cranial courses and branching pattern of the olfactory, optic, trigeminal, facial, cochlear, vestibular, glossopharyngeal, vagus, and hypoglossal nerves. All the articles pay special attention to the surgery on these nerves and the difficulties found to repair or to access neighboring areas after injury or disease.

Next, I will briefly describe the key topics of the first volume of Special Issue papers on cranial nerve investigation: Ontogeny/Phylogeny. However, the lessons we can learn from this first volume of the present Special Issue on Cranial Nerves of The Anatomical Record have profound implications for the matters raised in the second volume (Morphology/Clinical Significance). Many reasons have been argued to explain why the cranial nerves are like they are. One of the most powerful explanations has to do with the way our bodies are organized. And in turn, to know about how our bodies are, means to tell an evo-devo story.

The vertebrate head is the consequence of one more twist to the cephalization problem in nature. It is generally agreed today that the appearance of paired sensory organs and other structures in the frontal part of the head led the transition from filtering animals without brain to animals with a clear predator behavior (a certainly old idea known as the “new head” (Gans

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and Northcutt, 1983). This thought has been enriched in the last years with the novel view that the use of existing tissues, cell populations, and gene networks has also played a role (Manzanares and Nieto, 2003). This reuse may explain the development of cranial bone and cartilage, and sensory organs, but also the muscles populating the new head. This more global vision also includes a new perspective: these structures have co-evolved in a coordinated and integrated way for not only the head but also the neck, the heart, and the gastrointestinal tract (Diogo et al., 2015). Finally, this perspective agrees that the neural crests, the neural placodes, and the cardiopharyngeal field (CPF) are the original structures from which our craniofacial structure derives. Our head, neck, heart, and gastrointestinal tract seem to be the result of a continuous interaction between neural crest, placodes, and CPF, with ectodermal signals from the surrounding tissue during development. This way, crests, placodes, and CPF show dual interaction, as they display an instructive ability for the surrounding tissue, as well as they show plasticity to respond to certain instructive signals from the same surrounding tissue (reviewed by Manzanares and Nieto, 2003). And, what do these structures (skull, face, jaws, neck, heart, and gastrointestinal tract) have in common? One common feature is the presence of cranial nerves. And what do they have of special head, neck and heart, in comparison with the rest of the body, so that the former require the participation of the cranial nerves, in comparison with, say for example, the spinal nerves? Of course the brain, the main character of the cephalization process.

Briefly, the above-mentioned new paradigm shows that the brain seems to have conditioned the evolution of a protective skull ad hoc, as well as a face, and their sensory organs and muscles in a coordinated way with the proper brain functions of each taxa (Adameyko and Fried, 2016). This is relevant because several diseases that occur with cerebral malformation, also develop problems of facial development and, consequently, problems of shape and function of the face. It is revealing that several of these diseases occur with severe impairments of cranial nerve development, like human trisomy (Reid et al., 2015). In the same way, DiGeorge syndrome occurs with craniofacial and cardiovascular malformation, probably due to their coordinated development and to share stem cell populations with overlapping roles (reviewed by Diogo et al., 2015).

Furthermore, there is a body of evidences directly suggesting that the size and shape of the brain coevolved with the patterning of the base of the skull (reviewed by Marcucio et al., 2011), and this patterning takes place in parallel to the development of the cranial nerves. Certainly, a physical interaction between the developing brain and the bone, the cartilage, and the mesoderm exists (Richtsmeier and Flaherty, 2013). The frontonasal ectodermal zone (FEZ), an anterior region driving ectomesenchymal cells function through regional release of morphogens, and considered as a facial organizer, maintains a constant cross-talk with the developing brain. This cross-talk is crucial for both the brain and craniofacial development and is highly dependent on region-specific secretion of Sonic hedgehog (Shh), as differences in the physical relationship between the Shh-releasing forebrain regions and the Shh-sensitive FEZ areas may solely account for the differences in the facial structure between mammals and birds (Hu et al., 2015), and disruptions of this interaction lead to holoprosencephaly (Chong et al., 2012). A good example of this intimate interaction is the developing eye and the orbit. The eye is another craniofacial development organizer, and cross-talk between the extra-ocular muscles, the orbit-generating developing bone, and the developing eye through retionic acid and Shh has been demonstrated as a key interaction (reviewed by Adameyko and Fried, 2016).

The conclusion is that the head, the neck, the heart, and the gastrointestinal tract coevolved for cephalization through a developmentally integrated coordination of the activity of the neural crest, neural placodes, and the CPF. This coevolution also required a continuous mutual interaction between brain and bone, cartilage, and mesoderm (to drive the development of sensory organs and muscles). As the concentration of these tissues, cell types, and gene networks specialized in processing the most complex information ever is maximum in the cephalized anterior part of the body, this sole complex interaction drive the complex ontogeny and organization of the cranial nerves.

If all this was not enough, novel roles for cranial nerves have been described recently that are absolutely relevant to understand the organization of cranial nerves and some associated diseases. A number of works have clearly pointed to cranial nerves as crucial in craniofacial development by providing both morphogenetic signals and nerve-associated stem cells (Schwann cell precursors) traveling through these nerve highways to the innervation target. These stem cells contribute to both craniofacial development and adult regeneration, when required (reviewed by Adameyko and Fried, 2016). As a tissue development example, the trigeminal ganglion development requires a coordinated population of cells from neural crest and the ophthalmic and maxillary placode of the trigeminal nerve, at the same time when ectomesenchymal signals from the future sphenoid bone interact to determine trigeminal neuron gene expression (Hodge et al., 2007; Schlatterer, 2010). A similar body of evidences exists for teeth innervation (Zhao et al., 2014), taste bud formation, and the role of VIIth and IXth cranial nerves (Oakley and Witt, 2004), hair follicle (Brownell et al., 2011), cornea (Ueno et al., 2012), and salivary gland (Schutz et al., 2008), among others (reviewed by Adameyko and Fried, 2016). As for stem cells, it is important to consider first that the outgrowing nerve fibers of the cranial nerves have been described as highways for multipotent neural crest-like cells traveling to their target areas during development (Pagella et al., 2014). Second, these Schwann cell precursors change later their phenotype to neurons (Espinossi-Medina et al., 2014), thereby populating the innervation target after a trip through the cranial nerves and then differentiating into the postganglionic cells connected to the preganglionic axons they travel on (reviewed by Adameyko and Fried, 2016). Furthermore, during adult life, cranial nerves still serve as a reservoir of neural crest-derived peripheral glial cells that have been described contributing to regeneration in several models (reviewed by Kauca and Adameyko, 2014). Malfunctioning of this homeostatic, self-repair adult system is under a number of peripheral nerve-related pathologies (Kauca and Adameyko, 2014). All this together, it is clear the great relevance and close dependence of
involving, from a common point of view, the basic
neuroanatomy, the comparative anatomy, and the de-
velopment of the cranial nerves, as well as their branches,
their courses and their physiology, to address the repair
of their injuries and diseases.

Therefore, the field of cranial nerves is at present at a
crucial point. This Special Issue of *The Anatomical
Record* compiles works in the above mentioned Ontogeny/
Phylogeny and Morphology/Clinical Significance topics.
The organizational/developmental point of view (Volume
1 of this Special Issue) is populated with the long debated
cranial pair 0 or nervus terminalis (Peña-Melían et al.,
2018), the very atypical and interesting features of the
olfactory nerve (Crespo et al., 2018), the development and
pathologies of optic nerves (Herrera et al., 2018), the orga-
nization and function of the oculomotor complex in differ-
ent vertebrate brains, and the complex evolutionary
relationships derived from the comparative analysis of
eye muscles innervation (Company et al., 2018; Ferran
and Puelles, 2018), the anatomy and physiology of the
auditory portion of the VIIIth nerve and the segmental
organization of vestibular complex afferents and efferents
(Carricondo and Romero-Gómez, 2018; Diaz and Puelles,
2018), the atypical features of the spinal accessory motor
nerve and the present neuromeric brainstem concep-
tion (prosomicer model) after new data from the visceral
cranial nerve efferents (Puelles et al., 2018; Watson and
Tvrdik, 2018), and characterization of the cranial nerves
in lampreys (Pombal and Megias, 2018). This volume
1 Ontogeny/Phylogeny of the Cranial Nerves Special
Issue is completed with a historical overview of the cran-
ial nerves (Porras et al., 2018).

The Anatomical Record welcomes all this novel informa-
tion and the new points of view included in this Special
Issue, to approach the basic knowledge to the promotion of
endogenous self-repair capability and the experimental
therapies against a number of cranial nerve-associated
pathologies. While the extreme complexity and variability
of the cranial nerves throughout phylogeny and the com-
plicity of their ontogeny make understanding difficult, the
articles in this Special Issue of The Anatomical Record will
provide helpful insights to be closer to a solution. We can
be sure that by minding the heads of all the vertebrate
taxa and their ancestors, we will be able to take care of
our heads, and to alleviate or minimize the impact of
severe diseases or injuries affecting many people like that
of my old motorcycle friend.

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