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The segmentation of the human brain; a message to the neuroimaging community from an adjacent domain of the neurosciences

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ABSTRACT

Morphological and genoarchitectonic studies have conclusively shown that the human brain (and that of all vertebrates) is segmented i. e. is fundamentally composed of a number of rostrocaudally arranged brain segments or neuromeres. However in the current neuroimaging literature the term segmentation, derived initially from computer graphics technology, is used instead to indicate the neuroanatomical parcellation or subdivision of neural structures in the fully formed brain, especially the cortex. The neuroimaging community should be aware of the prior use of this term in the parallel discipline of neuroembryology, and should use a different one e.g. parcellation to avoid any confusion between the two growing disciplines.

Segmentation and current neuroimaging

At the time of the last turn of the century, the term *segmentation* was introduced into the neuroimaging literature to designate a particular form of computer-aided parcellation of the cerebral gray matter (Momenan et al., 1997; Dale et al., 1999). The term was derived from the image processing and computer graphics literature, in which 'segmentation' refers to the process of partitioning a digital image. Gradually, this initial meaning of 'segmentation' has shifted, however, and in the current neuroimaging literature the pertinent term is used instead for attempts to identify parcels or regions or areas of gray as well as white matter by means of whatever kind of atlasing or parcellation technique. In what follows, I will argue that this semantic confusion is to be regretted, and that it would be even preferable to avoid the use of the term 'segmentation' entirely in the neuroimaging literature.

Segmentation and current neuromorphology

In biology, the term *segmentation* specifically refers to the fact that some groups of invertebrates (annelid worms, arthropods) consist of a series of rostrocaudally arranged ring-like segments or metameres, within which several organ systems, including the central nervous system, repeat themselves. Vertebrates are also segmented. The segmentation manifests itself primarily in the paraxial mesoderm, which forms bilaterally a rostrocaudally arranged series of somites, each of which differentiates into a myotome (giving origin to muscular tissue), a dermatome (which gives origin to integumentary tissues) and a sclerotome (concerned in the development of the axial skeleton). By the end of the nineteenth century, it was well known that the early embryonic vertebrate brain also shows clear signs of segmentation (Orr, 1887; Locy, 1895; Hill, 1900). The brain segments, or neuromeres, present themselves as bulges separated from each other by external transverse constrictions (Fig. 1A and B). Initially, little attention was paid to these neural segments. Some authors, among them Neal (1918) and Streeter (1933), contended that these local widenings of the neural tube were artifacts, or caused by mechanical deformation of the tube imposed by adjacent structures. Moreover, it was generally held that the vertebrate brain is fundamentally composed of longitudinally oriented zones, which represent structural as well as functional entities (Johnston, 1902; Herrick, 1910), rather than of transversely arranged neuromeres (to which no functional significance whatever could be attributed).

In 1954, the Swedish neuroembryologists Harry Bergquist and Bengt Källén published under the modest title "Notes on the Early Histogenesis and Morphogenesis of the Central Nervous System in Vertebrates" a landmark paper that introduced a real paradigm shift, although this was by no means realized at the time of its appearance Bergquist and Källén (1954). Their publication was based on extensive embryological studies of representatives of all major groups of vertebrates. Focusing on patterns of cellular proliferation and migration, they found that in the ventricular zone of early embryonic brains, there are transversely oriented bands of

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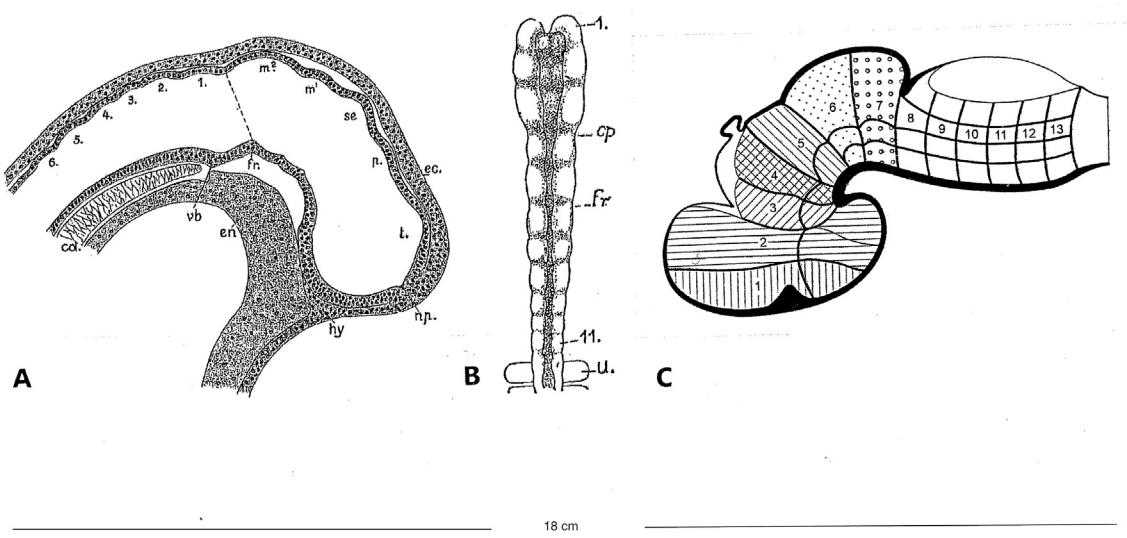

Fig. 1. Segmentation of the vertebrate brain. (A) Median section through the brain of an early salamander embryo. (B) Reconstruction of the neural tube of a chick embryo at 24 hrs of incubation. (C) Diagram showing the structural plan of the vertebrate neuraxis. A and B are reproduced from Von Kupffer (1906); C is modified from Bergquist and Källén (1954).

high mitotic activity that intersect with longitudinal zones showing similar proliferative features. By interference, a network made up of square domains of the brain wall displaying a high mitotic activity could be distinguished (Fig. 1C). During further development these proliferative areas form centres of radial migration into the developing mantle layer and were therefore designated as *migration areas*. The transverse bands (numbered 1 to 13 in Fig. 1C), which are oriented perpendicularly to the curved longitudinal axis of the brain, were shown by Bergquist and Källén to be equivalent to the neural segments or neuromeres described by previous authors (Fig. 1A and B). The Bergquist and Källén interpretation of the structures of the vertebrate brain, though initially fully ignored, has been spectacularly confirmed during recent decades by numerous studies of the expression patterns of a large number of developmental regulatory genes and their patterning products (morphogens, transcription factors) in the developing brain of various vertebrates (For reviews of this work, see Puelles, 2013; Puelles et al., 2013; Nieuwenhuys and Puelles, 2016; Nieuwenhuys, 2017.). It is now well established that the brain of all vertebrates is composed of a fixed number of neuromeres. Fig. 2 shows maps of the neuromeric subdivision of the brain of an adult lamprey, the most simple and primitive extant vertebrate (A), and of a human embryo of about eight weeks (B). In both brains each of the three primary brain vesicles, rhombencephalon, mesencephalon and prosencephalon, appears to be divisible into a number of neuromeres. The rhombencephalon consists of 11 rhombomeres (r1 - r11), whereas the mesencephalon comprises only two mesomeres (m1, m2). Rhombomeres and mesomers are separated by a separate isthmic neuromere (i), which is sometimes denoted as r0 (making a total of 12 rhombomeres). The prosencephalon consists of five neuromeres, the caudal three of which (p1 – p3) form the diencephalon proper. The two most rostral prosomeres are denoted as hypothalomo – telencephalic prosomeres 1 and 2 (hp1, hp2). As their names indicate, these two prosomeres participate in the formation of the telencephalon as well as the hypothalamus.

A molecularly defined zona limitans, or alar-basal boundary, extends throughout the brain, subdividing this structure and all of its constituent neural segments into separate basal and alar domains. Each of the neuromeres forms a complete ring of the neural tube including its own floor plate, basal plate, alar plate and roof plate sector. Rostrally, the left and right basal and alar plates are directly continuous across the median terminal wall (lamina terminalis) of the neural tube (Fig. 2). The intersecting boundaries of the neuromeres and the longitudinal alar and basal zones delimit, as already indicated by Bergquist and Källén, quadrangular progenitor domains, which represent the *fundamental morphological units* (FMUs) of the neuraxis. During early development these units are thin-walled, but later they grow considerably and transform into radially oriented structures, comprising neural derivatives extending from the ventricular surface to the meningeal surface of the neuraxis. These entities are denoted as fundamental morphological units because the major neural histogenetic processes, including cellular proliferation, -migration and -differentiation, as well as the formation of grisea (cell masses, nuclei and cortices) occur principally within their confines. Some cell masses are the product of simple radial migration of neuroblasts occurring entirely within the confines of a single FMU, but the constituent cells of most definitive nuclei in the human brain are the product of radial migrations, stemming from the germinative zones of two or more adjacent FMUs. Moreover, the 'intrinsic' cells of many nuclei are supplemented by contingents of neuroblasts, originating from the matrices of other, nearby or remote FMUs, attaining their target areas by tangential migrations. As the noted neuroembryologist Luis Puelles (2015) has said: "The cell masses in the brain are not just sitting there, indepently one from another as potatoes in a potato-sack; they all have their own specific radial FMU site(s) of origin and their own specific developmental history. Implying there is exquisitely controlled order in their final arrangement". It is the task of modern neuromorphology to identify the origins, differential identity and final position of all cell masses in the brain on the basis of their specific progenitor loci and the specific migration paths of their constituent neuronal elements. Because this type of analysis is predominantly based on the localization of genes or gene products it is designated as genoarchitectonics, and the resultant parcellation as genoarchitecture (Puelles and Ferran, 2012).

Conclusion

In the preceding section, a brief overview has been presented of the modern molecular approach to the parcellation of the grisea in the brain. It is shown that the human brain (and the brain of vertebrates in general) is segmented, and that the neural segments and their direct derivatives – the fundamental morphological units – play a crucial role in the development of the brain. Needless to say, the differentiation and segregation of the individual cell masses is not just a matter of segmentation but rather involve a variety of other developmental processes. However, considering the crucial importance of this intrinsic biological