

1 Overview of the Development of the Human Brain and Spinal Cord.	1
Hans J. ten Donkelaar, Shigehito Yamada, Kohei Shiota, and Ton van der Vliet	
1.1 Introduction	1
1.2 Major Stages in the Development of the Human Brain and Spinal Cord	2
1.3 The First 3 Weeks of Development	8
1.3.1 Implantation	8
1.3.2 Gastrulation	9
1.3.3 Folding of the Embryo	10
1.4 Neurulation	12
1.5 Development of the Spinal Cord	14
1.6 Pattern Formation of the Brain.	15
1.7 Early Development of the Brain	17
1.7.1 Imaging of the Embryonic Brain.	18
1.7.2 Neuromeres	19
1.7.3 The Ganglionic Eminences	21
1.8 Fetal Development of the Brain.	22
1.8.1 The Cerebellum.	22
1.8.2 The Cerebral Cortex	25
1.8.3 Cerebral Commissures	32
1.8.4 Imaging of the Fetal Brain	32
1.9 Development of the Meninges and Choroid Plexuses	33
1.10 Development of the Blood Supply of the Brain	34
1.11 Development of Fibre Tracts (Including Development of Myelination)	39
References	46
2 Mechanisms of Development.	53
Hans J. ten Donkelaar	
2.1 Introduction	53
2.2 Neural Induction	54
2.2.1 The Spemann-Mangold Organizer	54
2.2.2 The Molecular Basis of Neural Induction.	55
2.2.3 Polarity and the Establishment of the Neuraxis	56
2.2.4 Neural Induction in Amniote Embryos	57
2.2.5 Specific Pathways for Head Induction	57
2.3 Cell Lineage Studies and Fate Mapping.	59
2.4 Pattern Formation	60
2.4.1 Regionalization of the Forebrain.	65
2.4.2 The Zona Limitans Intrathalamica	66
2.4.3 The Midbrain-Hindbrain Boundary Organizer	66
2.4.4 Segmentation of the Hindbrain	67

2.5 Neurogenesis, Gliogenesis and Migration	69
2.5.1 Neurogenesis: Primary and Secondary Proliferative Compartments	69
2.5.2 Gliogenesis	72
2.5.3 Migration	75
2.6 Axon Outgrowth and Guidance	77
2.6.1 Pioneer Fibres	77
2.6.2 The Guidance of Axons to Their Targets	78
2.6.3 Axon Guidance at Choice Points	81
2.6.4 Commissure Formation	82
2.6.5 Formation of Thalamocortical and Corticofugal Projections	83
2.6.6 Formation of Topographic Maps	86
2.7 Programmed Cell Death	89
References	91
3 Causes of Congenital Malformations	105
Martin Lammens, John M.G. van Vugt, Michèl Willemsen, Patrick van der Voorn, Hans van Bokhoven, and Hans J. ten Donkelaar	
3.1 Introduction	105
3.2 Causes of Congenital Malformations	106
3.2.1 Genetic Disorders	106
Clinical Case 3.1. Meckel-Gruber Syndrome	113
3.2.2 Environmental Causes	114
Clinical Case 3.2. Cytomegalovirus Encephalopathy	118
Clinical Case 3.3. Amnion Rupture Sequence	119
3.3 Prenatal Diagnosis	120
3.3.1 Ultrasound and Magnetic Resonance Examination	121
3.3.2 Invasive Tests	126
Clinical Case 3.4. Traumatic Amniocentesis	128
3.3.3 Genetic Diagnosis	129
3.4 Inborn Errors of Metabolism Affecting the CNS	130
3.4.1 Inborn Errors of Metabolism That Mainly Affect the CNS	131
3.4.2 Multisystem Disorders with CNS Involvement	132
Clinical Case 3.5. Congenital Disorders of Glycosylation	135
Clinical Case 3.6. Walker-Warburg Syndrome	136
Clinical Case 3.7. Zellweger Syndrome	137
3.5 Myelination Disorders	139
Clinical Case 3.8. Histopathological Correlates of Radial Stripes on MR Images in Lysosomal Storage Disorders	140
Clinical Case 3.9. X-Linked Adrenoleukodystrophy	143
Clinical Case 3.10. Vanishing White Matter Disease	144
3.6 Vascular Disorders	145
Clinical Case 3.11. Porencephaly	148
Clinical Case 3.12. Twin-to-Twin Transfusion	149
Clinical Case 3.13. Punctate White Matter Lesions	150
Clinical Case 3.14. Multicystic Leukoencephalopathy	152
Clinical Case 3.15. Neonatal Alloimmune Thrombocytopenia	153
Clinical Case 3.16. Vein of Galen Aneurysm	154
3.7 Congenital Tumours	155
Clinical Case 3.17. Congenital Tumours: TSC	155
3.8 Classifications of CNS Malformations	157
References	158

4	Neurulation and Neural Tube Defects	165
	Hans J. ten Donkelaar, Mireille Bekker, Willy O. Renier, Akira Hori, and Kohei Shiota	
4.1	Introduction	165
4.2	Primary Neurulation	166
4.2.1	Primary Neurulation in Chick and Mammalian Embryos	166
4.2.2	Primary Neurulation in Human Embryos	170
4.3	Secondary Neurulation	173
4.4	Genetic Mouse Models for Neural Tube Defects	175
4.5	Aetiology of Human Neural Tube Defects	176
4.5.1	Genetic Basis: Neural Tube Defects as a Multifactorial Trait	177
4.5.2	Environmental Factors	178
4.6	Prenatal Diagnosis and Fetal Therapy	178
	Clinical Case 4.1. Prenatal Diagnosis of NTDs	179
4.7	Cranial Neural Tube Defects	180
4.7.1	Anencephaly	181
	Clinical Case 4.2. Ependymoblastomatous Exencephaly	185
4.7.2	Encephaloceles and Cranial Meningoceles	187
	Clinical Case 4.3. Occipital Encephalocele	190
	Clinical Case 4.4. Tectocerebellar Dysraphia	191
	Clinical Case 4.5. Cranial Meningoceles	192
	Clinical Case 4.6. Rudimentary Occipital Meningocele	194
4.8	Spinal Neural Tube Defects	196
4.8.1	Myeloceles, Myelomeningoceles and Spinal Meningoceles	197
	Clinical Case 4.7. The Spectrum of Deranged Neurulation	198
4.8.2	Spinal Lipomas	200
	Clinical Case 4.8. Spinal Lipomas	201
4.8.3	Spina Bifida Occulta and Related Disorders	203
4.8.4	The Tethered Spinal Cord Syndrome	203
	Clinical Case 4.9. Tethered Spinal Cord Syndrome	204
4.9	The Chiari Malformations	205
4.10	Caudal Dysgenesis	207
	Clinical Case 4.10. OEIS Complex	210
	References	211
5	The Neural Crest and Craniofacial Malformations	219
	Hans J. ten Donkelaar, Christl Vermeij-Keers, and Irene M.J. Mathijssen	
5.1	Introduction	219
5.2	Induction and Epitheliomesenchymal Transformation (EMT) of the Neural Crest	220
5.3	Derivatives of the Neural Crest	222
5.3.1	The Cranial Neural Crest	223
5.3.2	The Trunk Neural Crest	225
	Clinical Case 5.1. Congenital Aganglionosis	227
5.4	Craniofacial Development	228
5.4.1	Early Development of the Face	228
5.4.2	Development of the Pharyngeal Arches	230
5.4.3	Further Development of the Face	231
5.4.4	Development of the Skull	236

5.5	Neurocristopathies	238
5.5.1	Retinoic Acid Syndrome	239
5.5.2	Oculoauriculo-Vertebral Spectrum	239
5.5.3	Treacher Collins Syndrome	240
5.5.4	DiGeorge Sequence and Related Disorders	241
5.5.5	Waardenburg Syndrome	243
5.6	Cranial Ciliopathies	243
5.7	Holoprosencephaly	244
	Clinical Case 5.2. Alobar Holoprosencephaly	248
5.8	Abnormal Development of the Skull with CNS Manifestations	249
5.8.1	The Craniosynostoses	249
	Clinical Case 5.3. Prenatal Diagnosis of Apert Syndrome	254
	Clinical Case 5.4. Apert Syndrome	255
	Clinical Case 5.5. Thanatophoric Dysplasia	256
5.8.2	Cranial Base Abnormalities	258
	References	258
6	Development and Developmental Disorders of the Spinal Cord	271
	Hans J. ten Donkelaar, Kyoko Itoh, and Akira Hori	
6.1	Introduction	271
6.2	Gross Development of the Spinal Cord	272
6.2.1	A Few Notes on the Development of the Vertebral Column	273
6.2.2	Ascensus Medullae	274
6.3	Developmental Events in Spinal Neuronal Populations	275
6.4	The Specification of Cell Fates in the Spinal Cord	276
6.4.1	Specifcation of Neuronal Fates in the Ventral Spinal Cord	277
	Clinical Case 6.1. Spinal Muscular Atrophy	280
	Clinical Case 6.2. Hypoplasia of the Spinal Cord in a Case of Lethal Congenital Contracture Syndrome	281
6.4.2	Patterning Cell Types in the Dorsal Spinal Cord	282
6.5	Development of Dorsal Root Projections	283
6.6	Development of Spinal Ascending Projections	286
6.7	Development of Descending Projections to the Spinal Cord	288
6.7.1	Descending Projections from the Brain Stem	289
6.7.2	Development of the Pyramidal Tract in Rodents	291
6.7.3	Development of the Pyramidal Tract in Macaque Monkeys	293
6.7.4	Development of the Human Pyramidal Tract	294
	Clinical Case 6.3. Corticospinal System Reorganization	297
	Clinical Case 6.4. <i>L1</i> CAM Mutation	299
6.8	Developmental Anomalies of the Spinal Cord	299
6.8.1	Anomalies of Histogenesis	299
6.8.2	Duplications of the Spinal Cord	300
	Clinical Case 6.5. Diplomyelia	301
6.8.3	Neurenteric Cysts	302
	Clinical Case 6.6. A Spinal Intradural Enterogenous Cyst	303
6.8.4	Syringomyelia	306
6.8.5	Abnormal Course or Absence of Fibre Tracts	307
	Clinical Case 6.7. Absence of the Pyramidal Tracts	309
	Clinical Case 6.8. Anomaly of Decussation of the Pyramidal Tract in Trisomy 18	312
	References	313

7	Development and Developmental Disorders of the Brain Stem	321
	Hans J. ten Donkelaar, Johannes R.M. Cruysberg, Ronald Pennings, and Martin Lammens	
7.1	Introduction	321
7.2	Pattern Formation and Segmentation of the Brain Stem	323
7.2.1	Pattern Formation of the Brain Stem	323
	Clinical Case 7.1. Agenesis of the Mesencephalon and Metencephalon with Cerebellar Hypoplasia	326
7.2.2	Segmentation of the Brain Stem	327
7.3	Development and Developmental Disorders of the Cranial Nerves	329
7.3.1	Development of the Cranial Nerves and Their Nuclei in Rodents . . .	329
7.3.2	Development of Cranial Nerve Ganglia in Rodents	331
7.3.3	Developmental and Developmental Disorders of the Human Cranial Nerves	331
7.3.4	Congenital Cranial Dysinnervation Disorders	332
	Clinical Case 7.2. Congenital Cranial Dysinnervation Disorders . . .	339
	Clinical Case 7.3. Congenital Facial Palsy	340
	Clinical Case 7.4. Möbius Syndrome	341
7.3.5	The Sudden Infant Death Syndrome	343
7.4	Development of the Auditory System	343
7.4.1	Development of the Ear	344
7.4.2	Development of the Auditory Projections	349
7.4.3	Developmental Disorders of the Auditory System	350
	Clinical Case 7.5. Pendred Syndrome	352
7.4.4	Mutated Genes Involved in Deafness	353
	Clinical Case 7.6. Branchio-oto-renal Syndrome	359
	Clinical Case 7.7. Usher Syndrome	361
	References	362
8	Development and Developmental Disorders of the Human Cerebellum	371
	Hans J. ten Donkelaar, Martin Lammens, Pieter Wesseling, and Akira Hori	
8.1	Introduction	371
8.2	Some Notes on the Anatomy of the Cerebellum	372
8.2.1	Subdivision	372
8.2.2	Compartmentalization	373
8.2.3	Major Fibre Connections	373
8.2.4	Precerebellar Nuclei	374
8.3	Morphogenesis of the Cerebellum	375
8.4	Four Basic Steps in the Histogenesis of the Cerebellum	375
8.4.1	Characterization of the Cerebellar Territory	376
	Clinical Case 8.1. Cerebellar Agenesis	381
	Clinical Case 8.2. Rhombencephalosynapsis	382
8.4.2	Formation of Two Proliferative Compartments	384
8.4.3	Inward Migration of Granule Cells	385
	Clinical Case 8.3. Medulloblastoma	388
8.4.4	Differentiation of Cerebellar Neurons	390
	Clinical Case 8.4. Cerebello-Cortical Heterotopia in the Dentate Nucleus	392
8.5	Development of the Precerebellar Nuclei	393
8.5.1	Upper Precerebellar System	394
8.5.2	Lower Precerebellar System	394
8.5.3	Inferior Olivary Malformations	395

8.6	Mouse Mutants with Cerebellar Malformation	396
8.7	Developmental Disorders of the Cerebellum	397
8.7.1	Midline or Vermis Malformations	399
	Clinical Case 8.5. Dandy-Walker Malformation	403
	Clinical Case 8.6. Prenatal Diagnosis of DWM	405
	Clinical Case 8.7. Joubert Syndrome	406
8.7.2	Cerebellar Hypoplasia	408
8.7.3	Pontocerebellar Hypoplasias	409
	Clinical Case 8.8. Pontocerebellar Hypoplasia	410
8.7.4	Cortical Dysplasias	411
	Clinical Case 8.9. Dysplastic Cerebellum with Extreme Hydrocephalus	411
	References	412
9	Development and Developmental Disorders of the Forebrain	421
	Hans J. ten Donkelaar, Martin Lammens, Johannes R.M. Cruysberg, Karin Kamphuis-van Ulzen, Akira Hori, and Kohei Shiota	
9.1	Introduction	422
9.2	Prosomeres and Pattern Formation of the Forebrain	423
9.3	Development of the Diencephalon	426
9.3.1	Development of the Thalamus	427
9.3.2	Development of the Hypothalamus	433
9.3.3	Development of the Pituitary Gland	434
9.3.4	Developmental Disorders of the Hypothalamus and the Pituitary Gland	436
	Clinical Case 9.1 Duplication of the Pituitary Gland	438
	Clinical Case 9.2 Pharyngosellar Pituitary	439
	Clinical Case 9.3 Pallister-Hall Syndrome	440
9.4	Development of the Visual System	442
9.4.1	Development of the Eye	442
9.4.2	Congenital Malformations of the Eye	445
	Clinical Case 9.4 Aniridia	449
	Clinical Case 9.5 Retinitis Pigmentosa with CNS Malformations	450
9.4.3	Development of the Visual Projections	450
	Clinical Case 9.6 Isolated Absence of the Optic Chiasm	453
9.5	Overview of the Development of the Telencephalon	453
9.6	Development of the Rhinencephalon	461
	Clinical Case 9.7 A Remnant Olfactory Ventricle	466
9.7	The Prosencephalies	467
9.7.1	Aprosencephaly	467
	Clinical Case 9.8 Aprosencephaly	467
9.7.2	Holoprosencephaly	470
	Clinical Case 9.9 Prenatal Diagnosis of Holoprosencephaly	476
	Clinical Case 9.10 Holoprosencephaly with Hypertrophic Olfactory Nerves	478
	Clinical Case 9.11 Semilobar Holoprosencephaly with a Unique Traversed Coronal Sulcus	479
	Clinical Case 9.12 Middle Interhemispheric Variant of Holoprosencephaly	480
9.7.3	Septo-optic Dysplasia	482
	Clinical Case 9.13 Septo-optic Dysplasia	483
9.7.4	Isolated Arhinencephaly	483

9.8 Development and Developmental Disorders of the Basal Ganglia and the Amygdala	485
9.8.1 Development of the Basal Ganglia	485
9.8.2 Congenital and Acquired Disorders of the Basal Ganglia	492
Clinical Case 9.14 Selective Vulnerability of the Basal Ganglia	496
Clinical Case 9.15 Familial Striatal Degeneration (Glutaric Aciduria Type 1)	498
Clinical Case 9.16 Leigh Syndrome	499
9.8.3 Development of the Amygdala	501
Clinical Case 9.17 Urbach-Wiethe Disease	503
References	504
10 Development and Developmental Disorders of the Cerebral Cortex	523
Hans J. ten Donkelaar, Martin Lammens, Eleonora Aronica, Hans van Bokhoven, Karin Kamphuis-van Ulzen, and Akira Hori	
10.1 Introduction	524
10.2 Overview of the Cerebral Cortex	524
10.2.1 The Neocortex	524
10.2.2 The Mesocortex	526
10.2.3 The Allocortex	528
10.3 Overview of Main Cortical Connections	531
10.3.1 Thalamocortical Projections	531
10.3.2 The Pyramidal Tract	532
10.3.3 The Corpus Callosum and the Anterior Commissure	532
10.3.4 Long Association Fibres	534
10.4 Development of the Neocortex	536
10.4.1 Development of the Neocortex in Rodents	537
10.4.2 Development of the Human Neocortex	543
Clinical Case 10.1 Precocious Cerebral Development	555
10.5 Development of the Hippocampal Formation	557
Clinical Case 10.2 Temporal Lobe Dysgenesis	560
10.6 Development of the Main Cortical Connections	561
10.6.1 Development of Thalamocortical Projections	562
10.6.2 Development of the Pyramidal Tract	562
10.6.3 Development of the Corpus Callosum	562
10.6.4 Development of Long Association Fibres	566
10.7 Malformations of Cortical Development	566
10.7.1 Malformations due to Abnormal Neuronal/ Glial Proliferation/Apoptosis	567
Clinical Case 10.3 Extreme Microcephaly	571
Clinical Case 10.4 Microlissencephaly	574
Clinical Case 10.5: Tuberous Sclerosis Complex	575
Clinical Case 10.6 Hemimegalencephaly	576
10.7.2 Malformations due to Abnormal Cortical Migration	578
Clinical Case 10.7 Bilateral Periventricular Nodular Heterotopia	584
Clinical Case 10.8 Miller-Dieker Syndrome	586
Clinical Case 10.9 Subcortical Band Heterotopia	587
Clinical Case 10.10 Lissencephaly with Cerebellar Hypoplasia	589
Clinical Case 10.11 Walker-Warburg Syndrome	591
Clinical Case 10.12 Fukuyama-Type Congenital Muscular Dystrophy	594

10.7.3 Malformations due to Abnormal Cortical Organization and Late Migration	597
Clinical Case 10.13 Foix-Chavany-Marie Syndrome	598
10.7.4 Disorders of Cortical Development and Epilepsy	599
Clinical Case 10.14 MCDs and Epilepsy: TSC	603
Clinical Case 10.15 MCDs and Epilepsy: FCD	604
Clinical Case 10.16 Ammon’s Horn Sclerosis	606
10.7.5 Vascular Disorders	607
10.7.6 Disorders of Cortical Connectivity	607
Clinical Case 10.17 Assessing Prenatal White Matter Connectivity in Commissural Agenesis	610
Clinical Case 10.18 Callosal Agenesis	611
10.7.7 Intellectual Disability	613
Clinical Case 10.19 Severe Intellectual Disability and Neuronal Migration Defects due to Mutations in <i>DYNC1H1</i>	617
Clinical Case 10.20 Male Rett Syndrome	619
10.7.8 Neurobehavioural Disorders	620
References	623
Index	643