Chapter 9
Morphological Features of Human Dendritic Spines

Josué Renner and Alberto A. Rasia-Filho

Abstract Dendritic spine features in human neurons follow the up-to-date knowledge presented in the previous chapters of this book. Human dendrites are notable for their heterogeneity in branching patterns and spatial distribution. These data relate to circuits and specialized functions. Spines enhance neuronal connectivity, modulate and integrate synaptic inputs, and provide additional plastic functions to microcircuits and large-scale networks. Spines present a *continuum* of shapes and sizes, whose number and distribution along the dendritic length are diverse in neurons and different areas. Indeed, human neurons vary from aspiny or "relatively aspiny" cells to neurons covered with a high density of intermingled pleomorphic spines on very long dendrites. In this chapter, we discuss the phylogenetic and ontogenetic development of human spines and describe the heterogeneous features of human spiny neurons along the spinal cord, brainstem, cerebellum, thalamus, basal ganglia, amygdala, hippocampal regions, and neocortical areas. Three-dimensional reconstructions of Golgi-impregnated dendritic spines and data from fluorescence microscopy are reviewed with ultrastructural findings to address the complex possibilities for synaptic processing and integration in humans. Pathological changes are also presented, for example, in Alzheimer's disease and schizophrenia. Basic morphological data can be linked to current techniques, and perspectives in this research field include the characterization of spines in human neurons with specific transcriptome features, molecular classification of cellular diversity, and electrophysiological identification of coexisting subpopulations of cells. These data would enlighten how cellular attributes determine neuron type-specific connectivity and brain wiring for our diverse aptitudes and behavior.

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> "*When we say that the nervous system contains independent functional and morphological entities called neurons, we are saying much more than what appears at first sight. For, unlike the cells in most other tissues, the components of the nervous system are not equivalent and are not interchangeable parts. Each neuron is unique, and its singularity resides in its specific position in the nervous system. That position is given by its peculiar synaptic connections with other neurons and, either directly or indirectly, with the periphery. As the pattern of these connections is reflected in a rigorous fashion by the form of the neuron, its shape is its most properly neural feature. Thus, the form of a neuron provides the key to its role in the nervous system*" (Peters et al. 1991).

The study of dendritic spines in human neurons is a relatively recent occurrence adding to our knowledge about the "architectonic units of living things" (Peters et al. 1991). Spines were not initially recognized as actual cellular components, and several limitations still exist for visualizing these tiny specialized units with nanodomains in our nervous system. Nevertheless, there is a marvelous history of evolution for the emergence, development, functioning, and plasticity of dendritic spines and neural networks adapted for a myriad of different living species. The evolution of the brain structure, with specialized cells and circuits, provides cues on how complex processing and emergent functional properties let us be *Homo sapiens.* Humans have remarkable phylogenetic differences and ontogenetic development of dendrites, spines, and synapses. There are multiple implications for dendritic morphology for neural circuitry functioning. Spines are specialized elements that usually receive one axonal terminal forming an asymmetric synapse reflecting the excitatory input integrated within a time-space window. Multisynaptic spines also exist and add more complexity to this scenario. Dendritic spines are found from the spinal cord dorsal and ventral horns' neurons to higher-order neocortical areas, although showing heterogeneous numbers, shapes, and sizes. These morphological findings reflect the synaptic ultrastructure, pre- and postsynaptic features, and relevant functions for each neuron in its microenvironment (together with glial cells, extracellular matrix, and vasculature) and every neural circuit. Spines can be normally stable or plastic elements and altered in number, morphology, and ultrastructural composition along healthy aging processes or neuropathological conditions. Here, we discuss these topics and the findings that make dendrites, spines, and synapses key elements for the complexity of our brain and behavior, some showing unique properties in our species compared to other ones. Various examples of human neurons ranging from a very sparse presence to a high density of spines with varied shapes and sizes are presented with their likely functional relevance. Addenda were included to expand some key points with their original descriptions. In the end, perspectives are commented on methodological approaches aiming to expand our comprehension of the integrative role of dendritic spines in different functional networks and brain areas.

9.1 The Evolved Brain Structure: Cells and Circuits

Evolution and genetics are fundamental to unraveling the extraordinary development of what life on the Earth is and how organisms are organized for survival and reproduction while coping with a diversity of challenging conditions coming from a complex and contingent world (Schmidt-Nielsen 1997; Mayr 2001; Catania 2017; Leopold et al. 2019; Keough et al. 2023). Life lies in each detail of the orchestration of morphology, biochemistry, biophysics, and physiology. It relies on matter and energy, and the emergence of activity within a range of biological probabilistic possibilities after the integration of unitary functions that generate one sole body (Schrödinger 1992; Purves et al. 2001; see also Junker 2007). Cellular membrane, few ions relatively abundant in Earth´s crust, and an impressive variety of molecules and proteins compose different subcellular and cellular functional levels. Distinct neurogenic, immune, and developmental genes formed the cellular organization of ctenophores (Moroz et al. 2014) and the likely origin(s) of neurons (Burkhardt 2022). Evolution also provided emergent properties for integrated specialized nerve cells and the generation and modulation of complex functions and behaviors in different species. Emergent properties of nerve cells are more than just the sum of the properties of their parts. While function relies on the properties of each composing element, when assembled, the organized conjunct has more properties and can elaborate higher levels of activity (such as the isolated parts of an airplane that cannot fly but the conjunct does fly).

In addition, the nervous system is organized to elaborate behaviors and maintain a range of homeostatic adjustments, balancing change and stability, despite continuous multi-faceted external and internal variations, dealing with the acquisition, maintenance, development, and flexibility of adaptedness (Cannon 1939; Mayr 2001; Rasia-Filho 2006; Michael et al. 2009; Wefelmeyer et al. 2016; Rasia-Filho et al. 2018; Leopold et al. 2019). The morphological diversity and functional organization of neurons and glial cells reflect this major cellular specialization and connectivity achievements. Species-specific neural features involve ontogenetic changes, the animal´s notion of inanimate objects and who are the "others" (e.g., conspecifics, neutral cues, preys, or predators), elaboration of behavioral strategies for survival (Purves et al. 2001), and experience-dependent memory and learning (Kandel and LeDoux 2021; Shohamy et al. 2021). Epigenetic modulations of cellular functioning provide additional variability for cells and networks in individuals among the population (Kandel and LeDoux 2021; Burton and Greer 2022).

There are similarities in areas and connectivity in the central nervous system (CNS) of primates (e.g., Amiez et al. 2021). On the other hand, some patterns of synaptic organization are characteristic of each cortical area and show differences between species (DeFelipe 2011; Hunt et al. 2022). The nervous system´s connectional and functional organization increased along with the primate evolution (Holstege and Subramanian 2016; Sierpowska et al. 2022), and humans are considered outliers in terms of encephalization quotient (Herculano-Heuzel 2012). Interestingly, the most cognitively able brain is not the largest one

(Herculano-Heuzel 2012), but particular genetic features may have enhanced neurodevelopment, neuronal and glial structure, synaptic processing (e.g., for the glutamatergic one) in our species (Oberheim et al. 2009; Xu et al. 2018; Hodge et al. 2019; Beaulieu-Laroche et al. 2021; Berg et al. 2021; Viscardi et al. 2021; Pinson et al. 2022; An et al. 2023; Keough et al. 2023). It is likely that an increase in brain size with a folded cerebral cortex, the relative number and specialization of nerve cells, the connectional organization and type of synaptic processing, and the plasticity and metaplasticity of different networks formed the route that led us to *Homo sapiens* (based on Cajal 1894; Azevedo et al. 2009; DeFelipe 2011; Geschwind and Rakic 2013; Marín-Padilla 2014; Bruner et al. 2017b; Van Essen et al. 2018; Rasia-Filho et al. 2021; Schmidt and Polleux 2022). These improvements might have developed our ability to interpret and manipulate the external milieu, elaborate on more complex social relationships, and develop intellectual creativity leading to language, successful and progressively more complex inventions, our culture and arts, and the ability to transmit and judge information across generations[1] (Creutzfeldt 1995; Mayr 2001; DeFelipe 2011; Freiwald 2020; Rasia-Filho et al. 2021).

The integrated processing of information involves morphologically and functionally heterogeneous neurons and glial cells organized according to the cytoarchitectonic features of each region in the CNS. Dendrites and spines will be detailed in the next sections, but cell body and axonal features deserve attention as well. The neuronal cell body includes the nucleus, the perikaryon with organelles, and the plasma membrane with biophysical properties to integrate signals coming from dendrites and from direct axosomatic synaptic contacts. The neuronal input/output function not only depends on the somatodendritic morphology but also on the axon initial segment (AIS) origin, length, and position (Höfflin et al. 2017). "Axon-carrying dendrites" were discovered in CA1 pyramidal neurons of mice (Thome et al. 2014). Their occurrence and proportions are variable and type-specific in humans (Wahle et al. 2022). For example, in the CA1 hippocampal pyramidal neurons of adult humans, the axon emerges from the soma or from the initial portion of a basal dendrite (Benavides-Piccione et al. 2020). Changes in the length and position of the AIS location for action potential (AP) generation can impact the neuronal overall level of excitability and output code within neural circuits (Wefelmeyer et al. 2016). In layer V thick-tufted pyramidal neurons, the axon hillock location relative to the soma or a dendrite is finely tuned and related to the somatodendritic capacitive load (Hamada et al. 2016).

It is not completely known how axonal structural plasticity and changes in excitatory and inhibitory contacts upon dendritic shafts and spines cooperate to homeostatically adapt activity at the single-cell level. However, there is a continuous

[1] "Clearly, only humans sit around the fire (or dinner table) to tell each other jokes and stories about past glories or future plans, and only a human would eagerly read what Owen wrote about primate brains 140 years ago. Moreover, only humans use general engineering skills to overcome environmental challenges that other animals can solve solely through evolution by natural selection. These are, of course, merely some of the major differences between human" and other animals (Striedter 2004).

coordination of the formation, maintenance, turnover, strength, and plasticity of the presynaptic and postsynaptic partnered components (Stuart et al. 1999; Bourne and Harris 2007; Wefelmeyer et al. 2016; Kasai et al. 2021). Axonal arbor structural remodeling may involve presynaptic boutons dynamics and the possibility for changes related to postsynaptic plasticity (Wefelmeyer et al. 2016). Synaptic nanomodules underlie the organization and plasticity of discrete and aligned modules of pre- and postsynaptic proteins, whose number scales linearly with spine size (Hruska et al. 2018). Neural cells would then combine varied routes for synaptic plasticity and modulate their input–output relation and excitability in plastic circuits.

9.1.1 Dendritic Morphology

Dendrites have an arborized aspect that greatly increases the membrane available for synaptic contacts, information integration, and network functioning (Stuart et al. 1999). Dendrites represent the highest neuron's receptive surface area (approximately 93%; Torikai et al. 1996), receive most synaptic contacts, compartmentalize information, and integrate inputs along an extensive arbor (Kubota et al. 2007; Spruston et al. 2013). Accordingly, dendrites process most excitatory, and to a lesser extent inhibitory, synaptic inputs usually terminating on dendritic spines and shafts, respectively (Peters et al. 1991; Pannese 2015; see further results in Brusco et al. 2014).

Neurons differ in how their dendrites branch within the neuropil volume and how they receive incoming synaptic information from different afferent sources (Ramón-Moliner 1962; Rollenhagen and Lübke 2013; Benavides-Piccione et al. 2020). The geometry, extension, and three-dimensional (3D) spatial projection of dendrites critically determine the mode of neuronal connectivity within neural circuits (Peters et al. 1991; Rollenhagen and Lübke 2013; Guerra et al. 2023), that is, dendrites can receive a great number of afferents from a wide variety of sources and be highly integrative or, on the other hand, receive inputs from only one or at most a few sources and process a limited range of information (Peters et al. 1991). Afterward, dendrites integrate these inputs and provide synaptic responses of slower and faster time courses, filtering or amplificating signals (Bullock 1979; Stuart et al. 1999; Segev et al. 2003). These response features vary with (1) the pattern of activity in the afferent fibers; (2) the structure of the dendritic tree and location of the synaptic input; (3) the types and actions of synaptic transmitters receptors; (4) the intrinsic membrane properties and slopes of passive and active input–output curves; and (5) the biophysical and biochemical compartmentalizations or cooperativity effects of spines across dendritic segments (Bullock 1979; Peters et al. 1991; Harvey et al. 2008; Sjöström et al. 2008; Spruston et al. 2013; Sala and Segal 2014).

Furthermore, the dendritic number, branching pattern, and size of the field covered by the arborization identify a spectrum of neuronal types and subdivisions (Ramón-Moliner 1962). Morphological diversity of dendrites occurs even within the same neuronal class (Cembrowski and Spruston 2019; Benavides-Piccione et al.

2021; Rasia-Filho et al. 2021). Dendrites adapt their shape to the particularities of the surrounding neuropil, including the tissue volume available, the local cellular density and package, and the spatial distribution of afferent axons, some with specific domains for connectivity (Morishima and Kawaguchi 2006; Larriva-Sahd 2014; Wang et al. 2018; Rasia-Filho et al. 2021). For example, cortical layers II/III (supragranular) pyramidal neurons do not have enough space and cannot have a long apical dendrite like layer V thick-tufted ones, whereas these latter cells differ in their apical and basal branching aspects according to their location within layer V (Morishima and Kawaguchi 2006). Indeed, in the rat frontal cortex, two populations of layer V pyramidal neurons projecting to the striatum differ in their dendritic morphology. Superficial layer V neurons show tufted or slender apical dendrites in layer I, but the same type of neuron in the deeper layer V has a reduced or absent apical tuft (Morishima and Kawaguchi 2006). Morphological differences between layers II/III and V pyramidal neurons mean connectional and electrophysiological particularities with functional implications, as described below.

The first attempts to classify neurons based on "dendroarchitectonic" organization also looked for a correlation between morphology and function, as follows: "The radiate dendritic pattern may well be related to an input of heterogeneous origin and/or to the presence of relatively widely spaced afferent terminal fibers, whereas afferent connections of more homogeneous origin, composed of closely spaced axons that frequently terminate in dense clusters or other specialized endings (relate to) the tufted dendritic pattern. This type of relationship may appear in two different ways: (1) axonal fibers distributed in one or more planes or 'floors' parallel to one another and traversed by dendrites with 'linear' orientation. (2) Dendrites with 'planar' orientation lying in one or more planes parallel to one another and traversed by a stream of parallel axons" (Ramón-Moliner 1962; Fig. 9.1).

Currently, neuron types have been classified into different subsets based on the cell body shape, dendritic number, branching pattern, presence, distribution, density and shape of spines, and axonal ramification and projection. It is possible to recognize the existence of general morphological types and intermediate forms of neurons, although virtually no two cells display matching dendritic trees (Ramón-Moliner 1962; see also a comment in Ascoli 2015). For example, dendritic heterogeneity is evident in pyramidal neurons (Cajal 1909–1911). The morphology of these cells differ along subcortical to neocortical areas or within the same cortical area and show distinct electrophysiological properties within the same or across cortical layers in humans (Benavides-Piccione et al. 2020, 2021; Moradi Chameh et al. 2021; Planert et al. 2021; Rasia-Filho et al. 2021).

Dendrites (with different patterns of branching, number of collaterals in each order, length, and preferential spatial extension within the neuropil volume) show phylogenetic and ontogenetic characteristics to receive a varied number of input pathways and harness them as sources of learning possibilities (Cajal 1909–1911; Sjöström et al. 2008; Benavides-Piccione et al. 2020). There is an activity-dependent reciprocal loop between synaptic plasticity and dendritic excitability (Sjöström et al. 2008). To uncover the structural organization of dendrites, spines, axons, glial

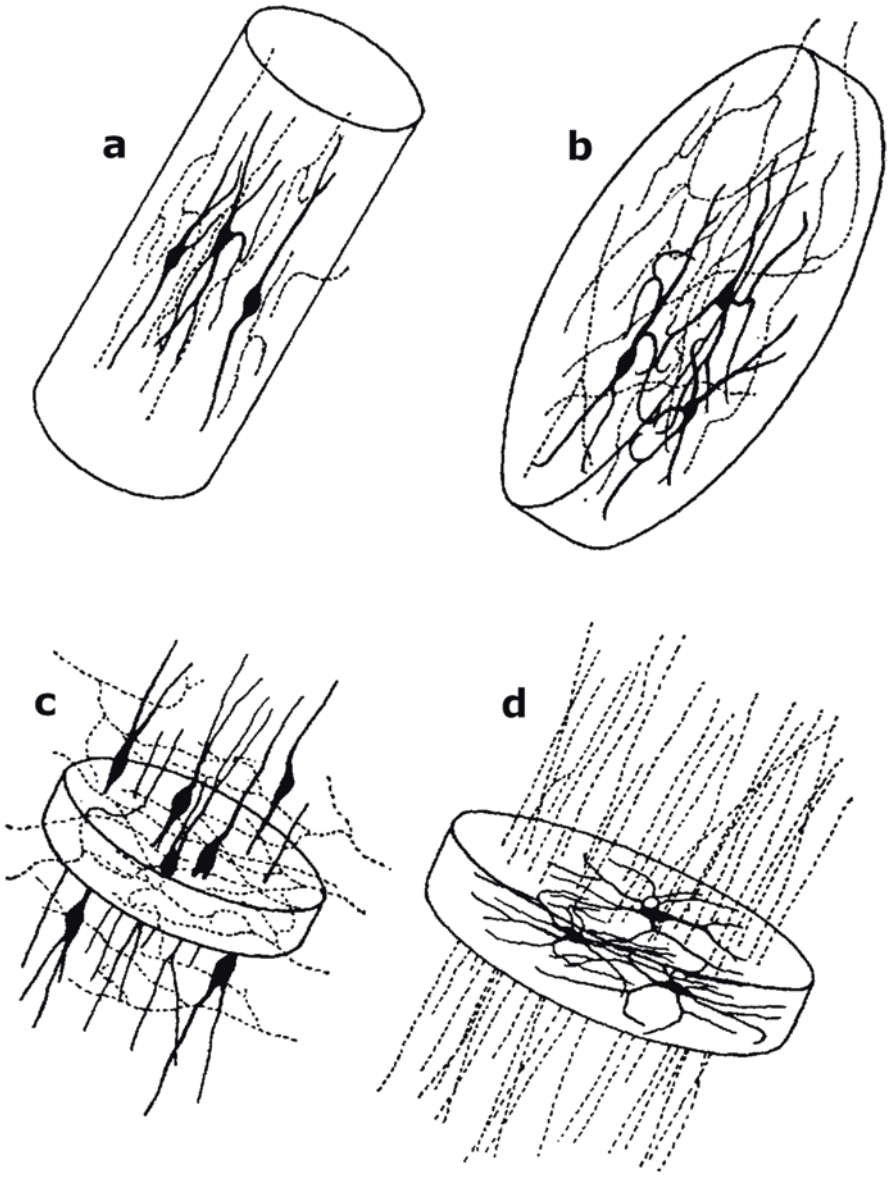

Fig. 9.1 Spatial orientation and contact of dendrites (emerging from the cell body and drawn in black) with axons (dashed lines) in the neuropil volume can show a (**a**) parallel linear (unidimensional) orientation, (**b**) parallel planar (bi- to three-dimensional) orientation, (**c**) linear orientation of dendrites perpendicular to the planar orientation of axons, and (**d**) linear orientation of axons perpendicular to the planar orientation of dendrites. (Legend adapted and figure reproduced from Ramón-Moliner (1962) under CCC RightsLink® license #5383310575621, originally published by John Wiley & Sons, Inc)

cells, and synaptic plasticity in the human nervous system is fundamental to understanding our wide neural wiring diagram and varied functional displays.

9.1.1.1 Wiring Properties Involving Dendritic Spines

Adapted to every CNS area, morphological and functional relationships make axons reach dendritic targets which, in turn, can also actively look for inputs and alter shafts and spine structure for the appropriate wiring of each microcircuit and large network. Dendrites and spines can be both under structural "renovation" and stability (Leopold et al. 2019, see the preceding chapters in this book). For example, both basal and apical dendritic architecture of CA3 and CA1 hippocampal pyramidal neurons show a spatial orientation and functional characteristic related to the local laminar connectivity and pathway of information processing (Andersen et al. 2007). The functional roles of dendrites for synaptic processing and integration were expanded by the existence of protruding spines forming postsynaptic multifunctional units (Shepherd 1996; Yuste 2010; Fig. 9.2). The multitude of spines added many more possibilities for processing synaptic inputs, adjoining a set of functional properties from micron to nanoscale dimensions and different time windows in dendritic arbors. Spines isolate each input and alter the impact of input potentials, expanding the integration and information processing of each neuron within local microcircuits and larger networks (Wefelmeyer et al. 2016). Inputs occur on dendritic spine postsynaptic density (PSD), whose structure and composition connect to a rich intraspine signaling machinery (Calabrese et al. 2006; Yuste 2010; Cohen 2013; Sala and Segal 2014; Nakahata and Yasuda 2018; Kasai et al. 2021). In these spiny cells, the synaptic signals reach different locations along the dendritic tree and find spines with diverse density, sizes, shapes, and stable or dynamic (plastic) features.

Fig. 9.2 Cortical synaptic organization. (**a**) Golgi-impregnated spiny stellate cell (shown in *a'* with the corresponding camera lucida drawing in *b'*) from lamina IV of the cat visual cortex. Both ascending and descending axons (ax) are observed in the neuropil. The vertically ascending axons are in specific synaptic relation with apical dendrites of pyramidal cells forming "synaptic cartridges." (*b'-e'*) There are multiple (longitudinal, oblique, and parallel) directions for the axonal fibers and ramifications (arrows) close to spiny dendrites (arrowheads). (**b**) Schematic diagram showing cortical inhibitory interneurons (in black) and pyramidal neurons. Note the spatial distribution of branched axons and the points of contact onto dendritic shafts and spines. (*a'-c'*) Drawings made from electron microscopic images showing synaptic types including an *en passant* synapse and an axon terminal contacting the same spine (*a'*), *en passant* axospinous and axodendritic synapses (onto a dendritic shaft, *b'*), and axosomatic synapses (*c'*) from different cortical layers (I-VI). Note the neuropil volume in this schematic representation. ap.den., apical dendrite; a.r., asymmetric membrane contact and round synaptic vesicles—putative excitatory synapses; a.t.c., axonal tuft cells; c.b.c., columnar basket cell; ch.c., chandelier cells; den, dendrite; l.b.c., large basket cell; pyr, cell body of a pyramidal neuron; s.b.c., small basket cells; s.f., symmetric membrane contact and flattened synaptic vesicles—putative inhibitory synapses. (Legends adapted and figures reprinted from Szentágothai (1978) under CCC RightsLink® license #1268521-1, originally published by Proceedings of the Royal Society of London, Series A, Mathematical and Physical Sciences)

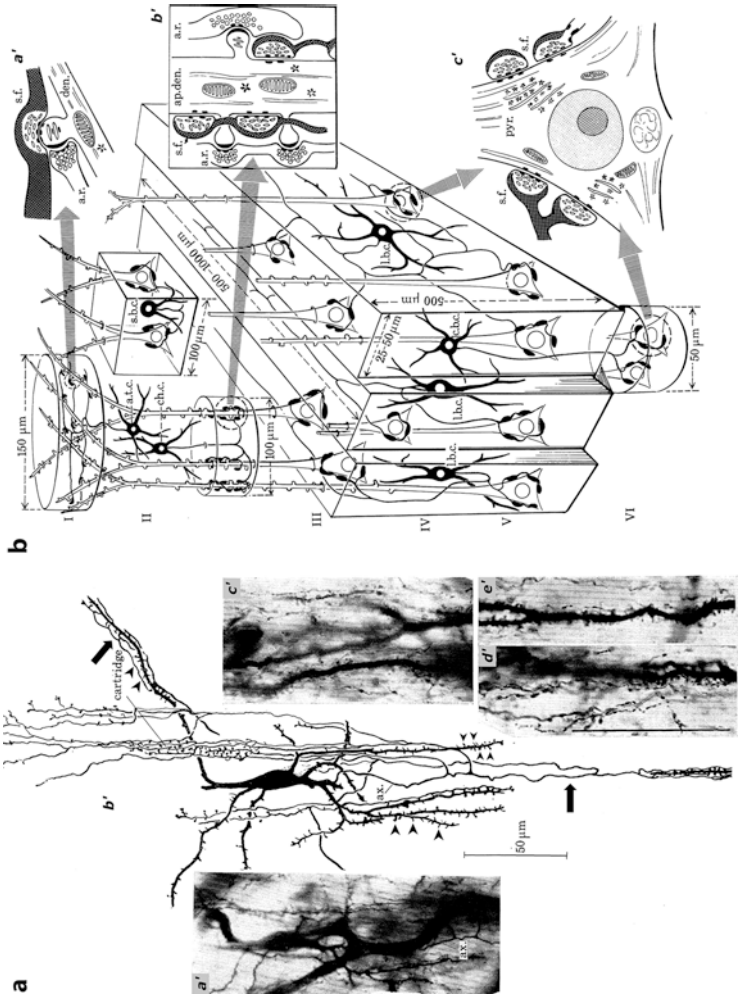

Fig. 9.2 (*caption on p. 374*)

Synaptic connectivity differs across neuronal types for optimal degrees of wiring and type of plasticity (Litwin-Kumar et al. 2017). Dendritic spines can modulate synaptic processing in multiple dendritic domains, reflecting different patterns of cellular connectivity (see Fig. 1 in Kubota et al. 2016), such as for memory encoding by hippocampal cells (Andersen et al. 2007; González-Ramírez et al. 2014; Larriva-Sahd 2014; Fig. 9.3). Furthermore, cortical pyramidal neurons with distinct basal and apical dendritic domains and synaptic receptive fields can (1) compartmentalize signals; (2) integrate input signals for synchronized transmission of information; (3) involve passive and active membrane properties and modulate synaptic strength; (4) generate anterograde depolarizations, be modulated by strategic inhibitory inputs, or be invaded by retrograde APs; (5) depending on intrinsic membrane properties, impose transient voltage changes that affect the dynamics of ionic diffusion caused by synaptic inputs; and (6) promote different impacts on the somatic excitability and neuronal firing pattern according to the frequency, time, and relative distance of synaptic inputs from the soma (Andersen et al. 2007; Sjöström et al. 2008; Yuste 2010; Spruston et al. 2013; Almog and Korngreen 2014). All these possibilities provide much more computational capabilities for the dynamic processing of information in spiny dendrites within circuits. In conjunction, the shape and function of human nerve cells reflect a complex development over millions of years of multicellular evolution.

Dendritic spines can be one of the key advances in the evolution of the nervous system and part of the way neural networks generate more elaborated emergent functional properties for neural networks (Yuste 2010; see also Brandon and Coss 1982; DeFelipe 2011; Rasia-Filho et al. 2021; Redgrave and Costa 2021). Dendritic spines maximize connectivity by accommodating a great number of distributed synapses (most excitatory) along the dendritic surface although using a minimal volume and containing a huge variety of molecules inside (Yuste 2010; Saga and Segal 2014; Ammassari-Teule et al. 2021; Helm et al. 2021). At the same time that dendritic spines can sample a wider choice of axons, they shorten the wire and condense input processing (Yuste 2010). By providing circuits with increased flexibility and computational power, different spiny neurons likely keep their functional influence distinct from one another by combining maximum connectivity with the functional individuality and modulation of each connection (Yuste 2010; Araya 2014).

Spines can establish contact with an *en passant* fibers, receive one single axon terminal, or be contacted by one or more axonal boutons from the same or different axons (Arellano et al. 2007b; Dall´Oglio et al. 2015; Shapson-Coe et al. 2021; Fig. 9.2). In the mouse cerebral cortex, most afferent axons contact just one spine in a dendritic segment, but a fewer and variable proportion of axons can contact two, three, or more spines of the same dendrite (see Fig. 6 in Kasthuri et al. 2015). Afterward, spines can integrate the action of several molecules in intraspine nanodomains, show varied tunable biophysical properties, promote biochemical compartmentalization, or allow the diffusion of small signaling messengers into the parent

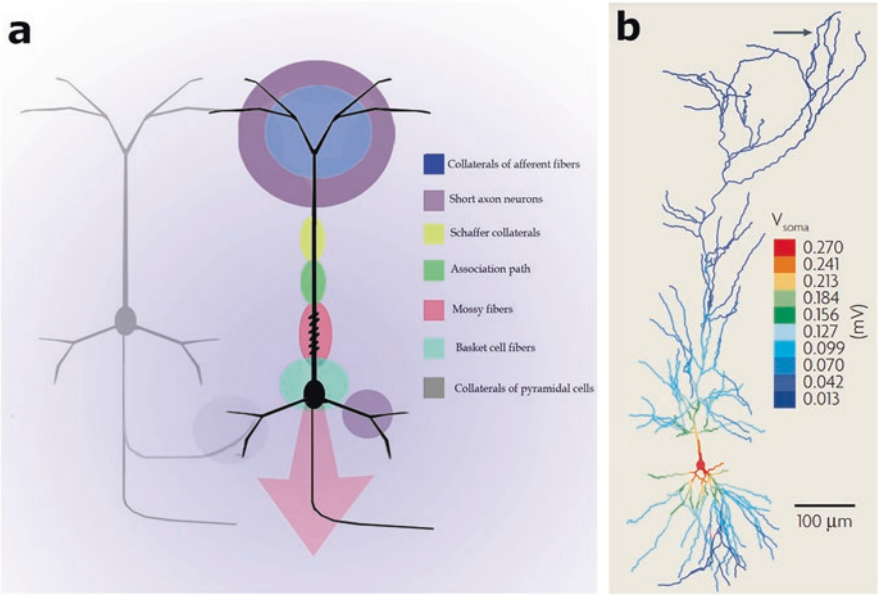

Fig. 9.3 (**a**) Schematic diagram of dendritic domains of a hippocampal pyramidal cell related to the distribution of different input sources (indicated by colors and to the right of this image) terminating along apical and basal segments. (Legend adapted and figure reprinted from Larriva-Sahd (2014) under CC BY license and Copyright © 2014 Larriva-Sahd). (**b**) Simulated attenuation of excitatory postsynaptic potentials (EPSP) on a CA1 pyramidal neuron depending on the dendritic location of synaptic inputs. The passive properties of dendrites make an excitatory synapse of fixed synaptic conductance (0.3 nS) proximal to the cell body promotes somatic amplitudes of 0.2–0.3 mV (colored yellow–red), whereas, in distal dendrites, the amplitude can be less than 0.02 mV (dark blue). The arrow points to a location where the local synaptic potential is approximately 13 mV and the resultant somatic EPSP is around 0.014 mV because of the small diameter and high impedance of distal dendrites. The presence of active properties in dendrites makes that synaptically induced EPSPs modulate the dynamics of voltage-gated channels, exhibit a nonlinear increased response, and lead to the occurrence of dendritic spikes. (Legend adapted and figure reprinted from Spruston (2008) under CCC RightsLink® license #5438800696086, originally published by Springer Nature)

dendrite (see the first chapter of this book).[2] In other words, on a spine-by-spine basis (Oray et al. 2006), there can be a high degree of synaptic modulation arising

[2] "In particular, the activity of one spine can modulate the plasticity of neighboring spines through the mutual sharing of plasticity-related proteins or through the activation of synchronized synaptic inputs. These changes occur across different time scales and typically result in the spatial organization of spines into groups or clusters. This phenomenon suggests that spines do not act as single functional units but are part of a complex network that organizes spines in groups to optimize the connectivity patterns between dendrites and surrounding axons" (Mijalkov et al. (2021) and references therein).

from spatiotemporal and functional heterogeneity among individual synapses on the same dendrite, between different neurons, and across and between brain regions. Synaptic diversity and strength are jointly adjusted to code information (Chen et al. 2011; Chabrol et al. 2015) from unimodal to multimodal inputs and from restricted or multiple parallel pathways (Soltesz and Losonczy 2018).

Importantly, the relationship between the structure and function of each spine depends on every area, circuit, synaptic demand, modulatory intracellular and extracellular factors, and species (Bourne and Harris 2007; Rochefort and Konnerth 2012; Yuste 2013; Hayashi-Takagi et al. 2015; Nakahata and Yasuda 2018; Zancan et al. 2018). Experimental data revealed that dendritic spines show activity-dependent structural remodeling that, together with molecular changes, impacts synaptic strength, learning, and behavioral displays (Harvey et al. 2008; Hayashi-Takagi et al. 2015; Wefelmeyer et al. 2016). In general, spines can (1) modulate excitatory postsynaptic potentials (EPSPs) mediated by AMPA and NMDA glutamate receptors using passive and active biophysical properties; (2) promote biophysical compartmentalization in single spines and provide varied voltage regimes toward parent dendrites (or be affected by them); (3) amplify postsynaptic responses by orchestrating different biochemical routes as signaling pathways at different timescales; (4) define biochemical microdomains that modulate intraspine calcium levels, actin phosphorylation, and second messengers availability, among other possibilities; (5) participate in the synaptic input modulation along diverse dendritic segments, including voltage cooperativity and molecular crosstalk between neighbor spines (with different properties along proximal to distal branches, main shafts, and collateral ones); (6) integrate synaptic signals within a spatiotemporal window for linear and nonlinear impacts on the somatic voltage and neuronal firing output; and (7) maintain a certain degree of isolation for each input or form groups making that each input have an activity-dependent synaptic weight and plasticity in integrated networks (Chen et al. 2011; Chen and Sabatini 2012; Spruston et al. 2013; Tønnesen and Nägerl 2016; Lu and Zuo 2017; Cornejo et al. 2022; see the first chapter of this book).

Spines may not be uniformly distributed along different dendrites; mixed spine types occur along the same dendritic segment, and spines can undergo plastic changes in their turnover, number, shape, size, spatial location, and clustering pattern (Wefelmeyer et al. 2016; Kastellakis and Poirazi 2019; Mijalkov et al. 2021; Rasia-Filho et al. 2021). Although general features identify neuronal types, there may exist intra-individual and interindividual variability in morphology, connectivity, electrophysiology, and function for the same cell class within networks.[3] In this

[3] Neuroanatomical and functional heterogeneity may exist within cortical areas and their subdivisions (e.g., see Vogt 2015) which refers to the surface location, macroscopic aspect, and dimension (e.g., Scheperjans et al. 2008; Bruner et al. 2014, 2017a, b); the corresponding function depending on experience, emotion, and behavior (e.g., in musicians, Gaser and Schlaug 2003; Omigie 2016; Bouhali et al. 2020); and variable gray matter width, heterogeneous cytoarchitectonic width, cellular composition, and neuropil package (Pandya et al. 2015; Mai et al. 2016; Triarhou, 2009 and the von Economo and Koskinas' atlas of cytoarchitectonics of the adult human cerebral cortex;

regard, some spines can also show dynamic features depending on the type of stimuli received and their functional role (González-Burgos et al. 2017). Spines can grow, retract, and shrink with a turnover rate (i.e., a balance between formation and elimination) in a time window that can vary between neurons and brain areas (Toni et al. 1999; Wefelmeyer et al. 2016). Indeed, results depend on the sampling and experimental procedures, and synaptic structure and function can be dynamically modulated at the single-spine level.

There are still many gaps in the elucidation of dendritic spines morphology and function in an inherently highly complex brain like ours. In the next sections, we describe and illustrate relevant findings regarding dendritic spines across different areas of the human CNS. These data address the long pathways that still need to be paved for understanding human spines at the same time that can direct future efforts with clinical implications.

9.2 Phylogenetic Specialization of Dendrites and Spines in Humans

Transcriptome analyses of invertebrate neurons revealed a complexity of synaptic and intracellular signaling pathways comparable to that of vertebrates, suggesting the existence of diverse ancestral presynaptic and postsynaptic pathways for neuronal functions and plasticity (Moroz 2011). On the other hand, the human brain is larger and contains more neurons than expected for a nonprimate mammal of its body size (Azevedo et al. 2009). Although human dendrites and spines have many evolutionary conserved features, they also show unique properties to transform synaptic inputs into complex functions within evolved circuits and brain areas.

Our brain composes only 2% of the adult body's weight but has a high metabolic and energy demand requiring over 15% of the cardiac output continuously (Leopold 2009; see further comments in Herculano-Houzel 2012). Our large cerebral cortex (82% of total brain mass) holds only 19% of all brain neurons (Azevedo et al. 2009). Therefore, more than building on an area by adding more and more neurons in a restricted brain volume, it is likely that cellular morphological and functional specializations had to be developed for wiring new connections and to generate higher mental abilities (DeFelipe 2011; Bianchi et al. 2013; Paredes et al. 2016; Rasia-Filho et al. 2021; Hunt et al. 2022). In other words, neural circuits evolved with additional functional features and increased complexity for information processing from more specialized cells. Species-specific variations in these features are found at the finest level of cell type and circuitry distinction (Striedter 2004; Shepherd and Rowe 2017; Eyal et al. 2016; Van Essen et al. 2018; Hodge et al. 2019; Hunt et al.

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note a distinctive layer IV in motor cortex discussed by Yamawaki et al. (2014); and for data indicating that "cortical functions should rather focus on circuits specified by functional cell type composition than mere laminar location," see Guy and Staiger (2017)).

2022; Schmidt and Polleux 2022). Discrete and continuous morphological and functional variations may coexist underlying cell-type diversity within networks (BRAIN Initiative Cell Census Network (BICCN) 2021). In this way, a cell type with heterogeneous elements would accomplish an additional set of functions. "In the case of cell types that repeat across space, such within-cell-type heterogeneity could facilitate the simultaneous execution of distinct computations through the same apparent circuitry" (Cembrowski and Spruston 2019). This is the type of subtle but meaningful neuronal specialization that would support progressively more complex and dynamic networks (Lodato and Arlotta 2015).

For example, pyramidal cell diversity enables parallel information processing in the hippocampus (Soltesz and Losonczy 2018), and human cells in this area show four different branching patterns of their spiny dendrites (Benavides-Piccione et al. 2020). The "within-cell-type heterogeneity may provide the hippocampus the intrinsic flexibility that is needed to meet the diverse and variable demands of the external world" (Cembrowski and Spruston 2019). They are also related to our personal memories, cognitive processes, and social behavior, which are all parts of our self-consciousness processes and daily life. These properties would also be applied to glial cells and their participation in synaptic processing. Morphological heterogeneity of astrocytes occurs in the human temporal cortex (Hodge et al. 2019), and human-specific subtype and different astrocytes were demonstrated in the human cerebral cortex (Oberheim et al. 2009; Matyash and Kettenmann 2010; see also the molecular and adapted morphological diversity of astrocytes in Endo et al. (2022), and the description that approximately half of the synapses have an adjacent glial process in the mouse somatosensory cortex in Kasthuri et al. 2015).

We display characteristic genetic architecture phenotype (Grasby et al. 2020) and complex features in cortical layers constituted by different cyto-, myelo-, receptor, and synaptic properties across allocortical and isocortical areas (Palomero-Gallagher and Zilles 2019). In the human temporal cortex layers II/III, which greatly expanded during evolution for increased cortico-cortical connectivity, pyramidal neurons are electrophysiologically heterogeneous and form five subtypes of cells with notable within-individual variability (Planert et al. 2021). Moreover, in the human middle temporal gyrus, layer V pyramidal extratelencephalic- and intratelencephalic-projecting neurons are morphologically distinct. The former type has an apical tuft terminating at the pial surface, a higher apical and basal dendrites total length and dendritic branches, a larger average diameter of the apical dendrite, and a greater total apical and basal dendrite surface area than the latter one (Kalmbach et al. 2021).

9.2.1 Some Differences Between Humans and Other Commonly Studied Species

Understanding the emergence of human higher cognition involves the elucidation of the evolutionary reason for the divergence in gene expression patterns in the human brain and the features that determine neuronal diversity and specialization in our

species (Geschwind and Rakic 2013; Hodge et al. 2019, 2020; Kalmbach et al. 2021; Schmidt and Polleux 2022). For example, human pyramidal neurons may have unique morphological and functional properties compared to other species (Mohan et al. 2015; Eyal et al. 2016). However, this is not an easy task. There may exist approximately 16 billion cortical neurons, 61 billion non-neuronal cells, and 180 areas per hemisphere bounded by specific cellular, functional, connectional, and topographic features in the human cerebral cortex (Azevedo et al. 2009; Glasser et al. 2016). For a brief comparison between species, the sea hare *Aplysia californica*, from which fundamental data on the cellular biology of learning and memory were obtained, has a nervous system composed of nine ganglia with approximately 10,000 neurons (Moroz 2011; Liang et al. 2019).

Rats and mice are some of the most studied animal models in the literature. Comparatively, there are morphological differences between the developing human and mouse neocortex (Geschwind and Rakic 2013), as well as in variations for the cortical microanatomical structure (thickness, layers, number of neurons, and synaptic profiles) between humans, rats, and mice (DeFelipe 2011). Large pyramidal extratelencephalic-projecting neurons in temporal cortex layer V are relatively abundant in mice, followed by macaques, and then humans, as evaluated using RNA FISH probes against conserved marker genes (Kalmbach et al. 2021). Neuron density decreased with brain enlargement making the number of synapses per neuron significantly higher as a function of brain expansion in neocortical areas of primates, including humans (Sherwood et al. 2020). There are also species-specific differences in the serotonin (5-HT) receptors and likely differences in the modulation of cortical activity in humans under both normal functioning and psychiatric disorders[4] (Hodge et al. 2019; Kalmabach et al. 2021; see a relevant discussion in Rust and LeDoux 2023).

[4] In the human and mouse temporal cortex, "the most-divergent gene families include neurotransmitter receptors, ion channels, extracellular matrix elements, and cell-adhesion molecules" (Hodge et al. 2019). There are "species differences in the expression of genes encoding 5-HT1 receptor family subunits. In mouse layer V extratelencephalic-projecting neurons, HTR1A and HTR1F were the dominantly expressed subunits, whereas, in human layer V extratelencephalic-projecting neurons, HTR1E (which is absent in the mouse genome) and HTR1F were highly expressed, with little HTR1A expression. These data suggest that human and rodent layer V extratelencephalic-projecting neurons likely share some similar distinctive intrinsic membrane properties and responses to neuromodulation in comparison to neighboring layer V intratelencephalic-projecting neuron types. In contrast, cross-species gene expression differences among layer V extratelencephalic-projecting neurons in mouse versus human highlight areas of potential phenotypic divergence" (Kalmbach et al. 2021). Therefore, extrapolations from animal models data on neuronal morphological, connectional, and functional features have to be done carefully when assuming similar implications to the human cerebral cortex (Hodge et al. 2019). Moreover, it is apparent "that genome-wide quantitative differences in expression profiles between species must also be considered when assessing the fine-tuned functional properties of a given cell type in different species... even classically defined, cerebellar cell types differ between mouse and human by expression of hundreds of orthologous genes... granule cell or astrocyte gene expression profiles can vary between species, or even in individual cells of a type, without losing their cell type identity. Studies of sixteen human *postmortem* brains revealed gender-specific transcriptional differences, cell-specific molecular responses to aging, and the induction of a shared, robust response to an unknown external event evident in three donor samples" (Xu et al. 2018).

Recent transcriptomic data also identified a highly diverse set of excitatory and inhibitory neuron types in the human middle temporal gyrus (Hodge et al. 2019). These data showed not only well-conserved cellular architecture across species that enables the matching of homologous types and predictions of properties of human cell types (Hodge et al. 2019, 2020) but also marked differences between homologous human and mouse cell types in proportions, laminar distributions, gene expression, and morphology (Hodge et al. 2019). The cumulative effects of such differences in the cellular patterning of genes relevant to neuronal signaling and connectivity might have shaped many differences in human cortical circuit function (Hodge et al. 2019) further tuned by a wide repertoire of plastic changes involving learning, emotions, creativity, culture, etc.

As noted above, humans display dendrites, spines, and synapses with crucial differences compared to other animals (Gioia et al. 1998; Elston and DeFelipe 2002; Schmidt and Polleux 2022). The structure of the human cerebral cortex characteristically show (1) larger neurons with more elaborated spiny dendritic trees, notably in (but not restricted to) the prefrontal cortex;[5] (2) thicker layers II/III, an overall larger neuropil, and more spacing between pyramidal neurons, which are the most abundant cells that compose the cortical gray matter; (3) expansion of pathways connecting cortical regions, including those from subcortical areas and between multimodal association areas; (4) more synaptic connections per cell (15,000–30,000 for layer II/III pyramidal neurons); (5) larger white matter volume, myelination, and increased connectivity between primary and unimodal association areas as well as between higher-order multimodal association areas; and (6) a high number and variety of local circuits neurons, most of which are inhibitory interneurons that critically control the pyramidal cells excitability (Elston et al. 2001; DeFelipe et al. 2002; DeFelipe 2011; Bianchi et al. 2013; Geschwind and Rakic 2013; Ardesch et al. 2019; Schmidt and Polleux 2022).

Many features characterize human cells as integrative devices with particular functional properties. Human neocortical pyramidal neurons show larger dendritic length and increased branch complexity with longer segments than mice, marmosets, and macaques (Elston et al. 2001; Mohan et al. 2015). Compared to chimpanzees, human cortical layer III pyramidal neurons are significantly longer and display more branched dendritic arbors in the primary somatosensory (Broadmann area, BA 3b), primary motor (BA 4), prestriate visual (BA 18), and prefrontal (BA 10) cortex, where exists the greatest dendritic complexity (Bianchi et al. 2013). Human pyramidal neurons from layers II/III of the temporal cortex have threefold larger dendritic length and increased branch complexity than similar cells in macaques and mice (Mohan et al. 2015). Likewise, an unusual subpopulation of calcium-binding

[5] The frontal, parietal, and temporal association cortices are larger in humans relative to those of other primates (Kolb and Whishaw (2021); see also Striedter (2004) for a critical discussion and findings on thalamic nuclei and cerebellar hemispheres, and Rasia-Filho et al. (2021) for a discussion on amygdaloid nuclei development with allocortex and neocortex evolved functions). The precuneus in the posteromedial parietal cortex is another cortical area with marked expansion in our species (Bruner et al. 2017a, b; see also Messina et al. 2023).

protein calretinin-positive pyramidal neurons is more abundant in the superficial part of layer V in the anterior cingulate cortex (ACC) of humans than in other primates (Hof et al. 2001).

Human layer V pyramidal neurons also display distinct compartmentalized responses and disrupted coupling between soma and distal dendritic domains compared to rodents (Beaulieu-Laroche et al. 2018). To compensate for the increased size of human dendritic arbors and attenuated signal integration over large distances, (1) neurons in deeper cortical layers show nonlinear properties for the summation of activity in multiple dendritic segments, whereas (2) those in superficial cortical layers reduced membrane capacitance (i.e., less depolarizing charge and fewer coactivated synapses are required for somatic firing) together with an increased propagation speed of APs for an enhanced signal transfer (Schmidt and Polleux 2022 and references therein). In addition, (3) human cortical neurons receive a higher density of synapses per dendritic segment when compared to various other species of primates or mice (Elston et al. 2001; Benavides-Piccione et al. 2002; Sherwood et al. 2020); (4) human synapses are structurally different compared to other species (Molnár et al. 2016; Yakoubi et al. 2019a, b, Rollenhagen et al. 2020) and provide higher information transfer rate by quickly recovering from depression after presynaptic AP train (Testa-Silva et al. 2014); (5) dendritic spines show many shapes and sizes expanding the possibilities for synaptic processing and plasticity (Yuste 2013; Araya et al. 2014; Dall´Oglio et al 2015); (6) human pyramidal neurons have a class of calcium-mediated graded dendritic APs that would classify linearly non-separable inputs, extending the signal processing/integration of connections and the repertoire of computations available to each cell (Gidon et al. 2020); and (7) human membrane properties amplify synaptically induced NMDA-dependent depolarizations (Hunt et al. 2022)[6] and significantly enable synaptic charge-transfer from dendrites to soma and axon (Eyal et al. 2016).

[6] Furthermore, "dendrites of layer II/III human pyramidal cortical neurons are more excitable, generating multiple dendritic Ca^{2+} spikes upon current injection. Dendritic APs in apical tuft dendrites were also found to be sharply tuned to specific input strengths... As a result, when inputs exceed optimal input strength, the amplitude of the dendritic Ca^{2+} AP is reduced. A striking consequence of this change in electrical properties of distal dendrites is that it enables human cortical pyramidal neurons to execute XOR logical operations in apical tuft dendrites, thereby extending the computational repertoire beyond simple AND/OR operations... As such, superficial and deep layer cortical pyramidal neurons may have evolved distinct mechanisms in response to the growing size of the cortex that depends on the computational role they play in the circuit. Each of these mechanisms may have enhanced the computational power in distinct ways. By increasing and tuning dendritic excitability of layer II/III pyramidal neurons, distinct logical operations can be performed on a dendritic level that otherwise would require the implementation of a complex neuronal circuit. In contrast, the isolated nature of distal dendrites in deep layer cortical neurons may provide a distinct compartment for parallel processing of information" (Schmidt and Polleux 2022).

9.2.2 *Evidence for Specialized Synaptic Processing in Humans*

Hunt et al. (2022) demonstrated that human synaptic connections are threefold stronger[7] and generate more reliable transmission than in mice when studying layer II/III spiny pyramidal neurons in the middle temporal gyrus (Brodmann area 21), part of the distributed cortical language circuitry. Associating compartmental models, *ex vivo* electrophysiological recordings, and morphology of postsynaptic cells, including synapses on the dendritic spine head, pyramidal-to-pyramidal connections in humans are associated with large AMPA- and NMDA-based conductances. The NMDA receptor activation in human neurons showed increased amplitude and prolonged decay of unitary excitatory EPSPs. This finding is important for neuronal excitability that, from a theoretical approach to quantifying properties of spinous synapses, indicates that a human-specific dendritic spine would generate synaptic conductance and voltage change threefold to fourfold larger than in mice (Hunt et al. 2022). Furthermore, considering a variety of spine morphologies and spine–neck values - which relates to spine–neck length and resistance, higher spine–head impedance, and decoupling of the spine head (and site of synaptic contact) from the spine base -, the unitary EPSP amplitude and the recruited NMDA conductance are larger in human versus mouse spines. Assuming that NMDA-dependent recurrent excitation might support persistent activity and working memory, these particular cortical microcircuits and spine properties would contribute to semantic and language processing stronger or unique to our species (Hunt et al. 2022; see further comment on the organization of neuronal circuits in the human brain in Schmidt and Polleux 2022).

Biophysical features of cortical layer V pyramidal neurons also differentiate our cells from other mammalian species. Human dendrites are "outliers" to other species' functional properties by exhibiting a high input resistance, a distinct suprathreshold behavior characterized by small and narrow spikes, low voltage-gated

[7] Accordingly, "the stronger connections in human are not due to a larger number of synaptic contacts. Rather, it is explained by the larger presynaptic active zones and PSDs in human that may allow higher release probability as well as more neurotransmitter release and binding (Benavides-Piccione et al. 2002; Yakoubi et al. 2019b), ultimately leading to larger synaptic conductance at human synapses" (Hunt et al. 2022). Specifically, "beside similarities, human synaptic boutons, although comparably small (approximately 5 μm), differed substantially in several structural parameters, such as the shape and size of active zones, which were on average 2 to 3-fold larger than in experimental animals. The total pool of synaptic vesicles exceeded that in experimental animals by approximately 2 to 3-fold, in particular the readily releasable and recycling pool by approximately 2 to 5-fold, although these pools seemed to be layer-specifically organized" (Rollenhagen et al. 2020). See additional relevant data comparing synaptic structure in humans and rats in Molnár et al. (2016). Importantly, layer-specific synaptic transmission structural parameter differences in temporal lobe layers IV and V, with larger values in layer IV, are suggestive of different neurotransmission efficacy, strength, and plasticity between human cortical layers (Yakoubi et al. 2019a, b). Human layer IV excitatory synaptic boutons may act as "amplifiers" of signals from the sensory periphery to integrate, synchronize, and modulate intra- and extracortical synaptic activity (Yakoubi et al. 2019b).

potassium and hyperpolarization-activated and cyclic nucleotide-gated channel (HCN)-mediated conductances (Beaulieu-Laroche et al. 2021). These data indicate that layer V pyramidal neurons in humans have a unique biophysical makeup for dendritic computations (Beaulieu-Laroche et al. 2021). The human larger dendritic trees of pyramidal neurons would track the activity of synaptic inputs with higher temporal precision to enable efficient information transfer from inputs to output within cortical circuits (Goriounova et al. 2019). These specializations in evolved neocortical cells and networks form a fundamental piece in the neural processing that brings about the spectrum of human behaviors. For neuronal populations, the confluence of molecular microscale architectural attributes (cell-type composition, morphology, and configuration in local circuits) and macroscale connectome architecture may be closely related to spatial patterns of evolutionary expansion, gene expression, intracortical myelin, cortical thickness, and laminar profiles - including spine number - and relate to different temporal dynamics and computations across cortical regions (Shafiei et al. 2020).[8]

In the human allocortex, hippocampal pyramidal neurons show a longer apical dendritic shaft, greater mean values of diameter, surface area, and volume, increased length of dendritic segments after branching, and more complex branching patterns than in mice (Benavides-Piccione et al. 2020; Fig. 9.4). Among other functions, the hippocampal neurons' structure and their synaptic plasticity are relevant for memory formation, consolidation, and retrieval, which are associated with interconnected brain areas to support our high levels of cognitive functions (Andersen et al. 2007; Basu and Siegelbaum 2015). The basal dendritic structure is more complex as a function of the distance from the soma in humans (Benavides-Piccione et al. 2020), which suggests that different dendritic domains in these neurons contribute to our functional features.

On the other hand, we do not have yet comparative data of this kind for human pyramidal neurons in subcortical regions, for example, those composing the amygdaloid complex. These neurons relate to the beginning of the great limbic lobe for higher cortical sensory perception and emotional elaboration, including interpretation of facial expressions and fear, and to evoke complex social behaviors in our species (Rasia-Filho et al. 2021; Guerra et al. 2023; see relevant data and concepts in Heimer et al. 2008; Rolls 2015; Freiwald 2020; Šimić et al. 2021; Rust and LeDoux 2023).

[8] For more information on human multimodal, higher-order processing and connected large-scale networks for the default mode and resting state, sensorimotor, executive control, subcortical and cortical emotional processing, detection of salience and attention, task-related and (abstract) cognitive activity, basal ganglia circuitry, and social behavioral display, see Goulden et al. (2014), van den Heuvel et al. (2015), Margulies et al. (2016), Ng et al. (2016), Diano et al. (2017), Bagarinao et al. (2019), Leopold et al. (2019), Bagarinao et al. (2020), Deming and Koenigs (2020), Shafiei et al. (2020), Bruton (2021), Hidalgo-Lopez et al. (2021), and Kolb and Whishaw (2021).

9.2.3 Human Dendritic Spines

As described above, spines are relevant to connectional, electrophysiological, and a large functional repertoire for the synaptic computations in dendrites. Cortical pyramidal neurons possess spines distributed from proximal to distal branches, along main shafts and collaterals (Feldman 1984; Ramaswamy and Markram 2015; Rasia-Filho et al. 2021). Only a small percentage of the axonal inputs to a neuron establish more than one synapse with the postsynaptic cell in the human cerebral cortex (Shapson-Coe et al. 2021). Therefore, spines can isolate inputs and also integrate the information from a larger number of inputs along the dendritic arbor (Yuste 2010). Compared among cortical areas, spine densities and branching patterns of layer III pyramidal cells increase from primary to higher-order cortical areas. This increase represents 2.6-fold more spines in the middle temporal area, 11-fold more spines in the inferior temporal cortex, and 16-fold more spines in the prefrontal cortex compared to the primary visual area V1 of the macaque monkey (Elston and DeFelipe 2002 and references therein). Cross-species comparisons demonstrated that neurons in the human prefrontal cortex have at least 23 times more dendritic spines than those in V1 of the macaque monkey, which likely reflects differences in the number of excitatory inputs to different cortical areas and species-specific differences in cortical function (Elston and DeFelipe 2002).

Human dendritic spines are also larger and longer and show higher densities in hippocampal CA1 pyramidal neurons and layers II/III pyramidal neurons in the temporal cortex than in mice (Benavides-Piccione et al. 2002, 2020; see also Eyal et al. (2018), and different parietal cortex spine data in mouse in Kasthuri et al. 2015; Fig. 9.4). In addition, subcortical and cortical human spines display a diversity of shapes and sizes coexisting along various dendritic segments, some notably convoluted and with complex forms that are not usually found so abundant in corresponding areas of mice and rats (Rasia-Filho et al. 1999; Brusco et al. 2010, 2014;

Fig. 9.4 Representative examples of CA1 hippocampal pyramidal cells from human (**a**) and mouse (**b**). The morphology of cells was studied using Lucifer Yellow microinjection, confocal scanning, and fluorescence microscopy. Neuronal reconstructions are presented at the same magnification to illustrate differences in cell size. The main apical dendrite (in black), apical collateral dendrites (in blue), basal arbor (in red), and axon (if traced, in green) are shown with the prevalence percentage of each morphological dendritic pattern found in the studied samples. (**c**) Schematic representation showing the different main apical branching patterns of these human neurons (exemplified in (**a**) and measured within the first 200 μm): *a'*, 0 - no bifurcation; *b'*, 1 bifurcation; *c'*, 2 bifurcations; and *d'*, 3 bifurcations. (Legend adapted and Figure reproduced from Benavides-Piccione et al. (2020) under CCC RightsLink® license #5383911347030, originally published by Oxford University Press). (**d**, **e**) Photomicrograph of horizontally projecting dendrites of neurons injected with Lucifer Yellow from the human (**d**) and mouse (**e**) temporal cortex. At higher magnification, spines along basal dendritic segments in human (**f**) and mouse (**g**) pyramidal cells show morphological differences. Note the smaller size of mice spines compared to larger and longer ones of humans. Scale bar = 45 μm in (**d**) and (**e**); 10 μm in (**f**) and (**g**). (Legend adapted and figures reprinted from Benavides-Piccione et al. (2002) under CCC RightsLink® license #5383920674577, originally published by Springer Nature)

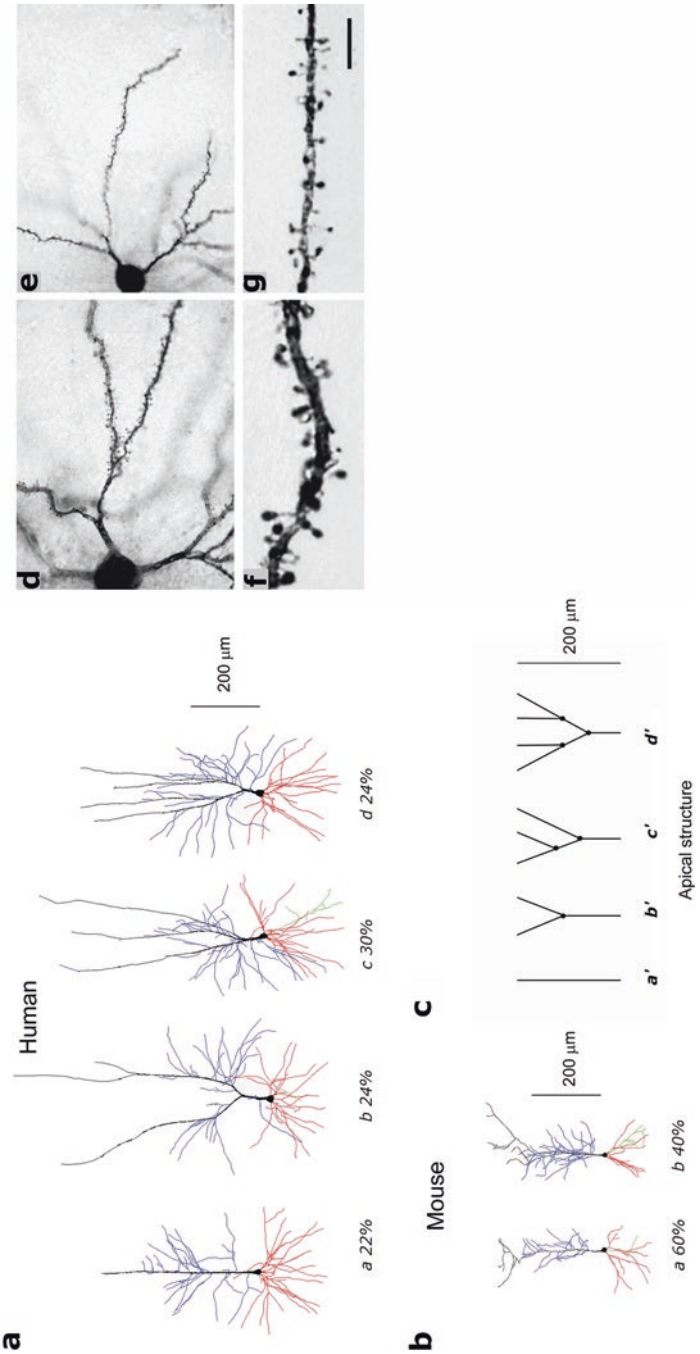

Fig. 9.4 (*caption on p. 386*)

Dall'Oglio et al. 2015; Becker et al. 2017). Taking into account the knowledge available from other species, these numerical and morphological features imply functional differences for the synaptic processing elaborated by human spines.

At the same time, cooperativity and actions among neighbor spines can lead to a wide range of modulatory and computational possibilities key to additional modulation of synaptic strength, integration, and plasticity (Nakahata and Yasuda 2018). Some spines alter the functioning of other neighbor spines within a spatiotemporal window for activity-dependent voltage changes and synaptically induced spreading of signaling molecules along parent dendrites. All these features increase the possibilities of neuronal computations and expand the possibilities of graded modulated functioning of synapses, spines, and dendrites for each neuron, more than a simple deterministic condition and with more possibilities in humans.

In addition, it is assumed that the head diameter in humans' larger spines would also relate to the extension of the PSD, the proportion of AMPA and NMDA glutamate receptors in the PSD, the subcellular cytoskeleton, the molecular composition, and the organelles present in the spine (e.g., actin for the spine structure and smooth endoplasmic reticulum (SER) to modulate intraspine and parent dendrite Ca^{2+} levels; Yuste 2010, 2013). The spine head diameter, PSD area, and its macular and perforated aspects relate to connection stability and structural plasticity in mushroom spines (Arellano et al. 2007a), occurring with selectivity after NMDA receptor-mediated long-term potentiation and depending on SER presence (Borczyk et al. 2019). Stubby and mushroom spines show similar average protein copy number and topology for PSD composition in cultured hippocampal neurons of rats, but proteins related to synaptic strength, spine dynamics, ion channels, endocytosis cofactors, cytoskeletal structure, signaling and trafficking, secretory proteins, and ribosomes are more evident in mushroom spines (Helm et al. 2021).

Human thin spines can show diverse sizes (Benavides-Piccione et al. 2013; Dall´Oglio et al. 2015; Vásquez et al. 2018), some displaying a long thin neck that ends in a bulbous head (Yuste 2013). Supposing a similar functioning in humans as in other species, the spine neck length and resistance can impose compartmentalization for both synaptically mediated electrical signaling and coupling with the adjacent dendrite (Tønnesen and Nägerl 2016). It can also affect the diffusion rate of calcium and small molecules from spines to the parent dendrite. Although long-necked spines can be found in rats (Rasia-Filho et al. 1999), they would provide further dynamic possibilities in the context of the human processing of information. Some human dendritic spines have neck lengths of about 30% longer and 100% more volume than in the somatosensory cortex of mice (DeFelipe 2011 and references therein). Dendritic spines that have longer necks may not generate significant depolarization at the soma, suggesting that EPSPs may be filtered in the spine neck. That may imply that long spines may be "electrically silent" and may be held in "reserve." By changing the spine neck to a shorter one, there might be a "plugging in" and, thereby, a fast circuit switching (Yuste 2013; see also Araya et al. 2014). Human neurons have higher spine densities and many spines with long necks, possibly indicating increased synaptic connectivity and plasticity (Yuste 2013). Following Cajal's descriptions of spiny human neurons and the quest to understand

the physical basis of human intelligence, spines displaying abnormally long necks have been seen in young patients with intellectual developmental disorders (Yuste 2013; see also von Bohlen und Halbach 2010 and further data below).

Ramified spines and multiform spines likely indicate a design for the existence of multisynaptic sites with microdomains/nanodomains that would interact when modulating information processing (Chen and Sabatini 2012; Stewart et al. 2014; Reberger et al. 2018). Multisynaptic spines would also relate to homeostatic plasticity and modulation of synaptic activity and demand levels (Wefelmeyer et al. 2016). Human spines of these types display a multitude of complex aspects with various stalk diameters, convoluted shapes, filamentous or thick parts, and various bulbous parts or endings (Dall´Oglio et al. 2015; Correa-Júnior et al. 2020; Rasia-Filho et al. 2021; Fuentealba-Villarroel et al. 2022; Guerra et al. 2023; note the aspect of spines in the "unipolar" neuron in Vásquez et al. 2018).

Because neighbor spines of varying shapes and sizes exist in the same dendritic segment, the morphological heterogeneity of spines even in a small portion of the dendritic shaft supports the possibility that synaptic strength is regulated at the level of every single spine (Frick and Johnston 2005; Arellano et al. 2007a, b, Chen et al. 2011; Lee et al. 2012; Rasia-Filho et al. 2021). These spine features provide a high computational capacity and activity-dependent regulation of synaptic strength for each neuron. Moreover, the presence of different spines in human pyramidal neurons is consistent with recent theories of synaptic learning. These synapses, which show gradation in states and are connected by plastic transitions, would confer an increase in storage capacity in neural networks (Lee et al. 2012; Dall'Oglio et al. 2015 and references therein). In humans, the synaptic processing of sensory, motor, emotional, thinking, and cognitive information reached a higher level adapted for our species-specific social behaviors. The presence, distribution, density, and shape of these spines are clear indications of neuronal connectivity (Cooke and Woolley 2005; Chen et al. 2011) with varied plasticity in each brain area (Toni et al. 1999; Hayashi-Takagi et al. 2015; Mohan et al. 2015; Bucher et al. 2020) and improved structural and encoding capabilities properties. These features would also relate to single-cell RNA-sequencing datasets that revealed particularities in gene expression, morphology, proportions, and laminar distributions of cell types in our cerebral cortex (Hodge et al. 2019) and species-specific differences in key molecules that regulate synaptic plasticity (Beed et al. 2020).

Axodendritic and axospinous synapses coexisting on the same dendritic segment and at different distances from the soma modulate the resultant neuronal excitability (Megías et al. 2001; Kubota et al. 2007; Spruston et al. 2013; Bucher et al. 2020). The phylogenetic development of spiny neurons has an evolutionary value in terms of increased connectivity and integrated functions by providing more computational possibilities and increasing complexity for synaptic processing in assembled cells. Spines add more plasticity to synaptic transmission, serving as time-space encoding and decoding devices for a moment-to-moment modulation of information processing. This kind of activity can be different along the human lifespan.

9.3 Ontogenetic Development and Changes in Dendritic Spines in Humans

Ontogenetic effects were reported for human cortical structure and, specifically, for dendrites and spines. Age relates to the development and dynamic reorganization of neuronal circuitries and synaptic connectivity (Jacobs et al. 1997; Dickstein et al. 2007; Petanjek et al. 2011, 2019; see Chap. 4 in this book). In this regard, the human cerebral cortex shows neoteny (delayed development) and heterochrony (different times for maturation) in circuits related to higher function elaboration (Geschwind and Rakic 2013; see additional data in Leopold et al. 2019). Large-scale networks involving brain connectivity and function have been recognized in the infant's brain (or their earliest forms, Smyser et al. 2010) to be matured with age and further changed in the elderly (Bagarinao et al. 2019 and references therein). Pyramidal neurons in cortical multimodal areas receive and process afferences from both local cortical non-pyramidal cells and from a broad range of synaptic inputs at higher association levels of integrative processing. These cells have longer and more branched dendrites as well as more spines than in areas that process a specific modality of activity (Jacobs et al. 2001; González-Burgos et al. 2019; Kolb and Whishaw 2021).

However, the study of the human brain's ontogenetic morphological and functional features is one of the most challenging tasks for our species. This is because many variables would modulate the fine-tuned shape and activity of neurons from the beginning of our development and continuing along the lifespan. Neuroglial plasticity relates to each personal history of life and culture, and this is valid for approximately 8 billion people living today. We all belong to the same species, and there is abundant genetic variation within humans making individuals display particular phenotypes and abilities (Mayr 2001). Neuroanatomical phenotypes can be partly heritable as well (Panizzon et al. 2009; Kremen et al. 2010). For example, from a large study in 51- to 59-year-old male twins, approximately 70% of the variance in the size of subcortical regions is determined by genetic factors (Kremen et al. 2010). The cortical thickness of prefrontal areas was among the most highly heritable, although individual-specific and not shared environmental factors can account for over 50% of the variance in the thickness of cortical regions (Kremen et al. 2010).

Cortical gray and white matter thinning and thickening change in different ways and regions over the course of children's development[9] and into old age (Kolb and

[9] "In the course of studying changes in gray matter, it has also been possible to distinguish group differences between healthy children and those displaying neurodevelopmental disorders (e.g., Giedd and Rapoport 2010). Fortunately, cortical abnormalities in children with neurodevelopmental disorders may not be permanent. Shaw et al. (2007) followed about 500 children, some typically developing and others with attention-deficit/hyperactivity disorder (ADHD). They found that reduced volume of gray matter in the prefrontal cortex was not permanent but rather reflected a delay in cortical development by about 2 ½ years, suggesting that ADHD is characterized by a delay rather than a deviance in cortical development... The association between delayed cortical

Whishaw 2021). A reduction in gray matter volume begins at 6–7 years of age and continues through adolescence, while white matter tracts and volume enlarge in the same period, likely related to neuron and synaptic pruning for improved functions in more efficiently connected circuits (Kolb and Whishaw 2021). As part of a brain developmental route, progressive changes with a reduction in gray matter density begin in primary areas (dorsal parietal and sensorimotor regions) and spread to secondary (spatial and language skills maturing at 11–13 years) and tertiary regions, such as the prefrontal cortex, maturing in late adolescence and continuing into adulthood (Kolb and Whishaw 2021). Later, in the human Heschl gyrus, *planum temporale*, primary visual cortex, gyrus parahippocampus, anterior insula, amygdala, and hippocampus, gray matter thickness decreased significantly with aging without differences between the left and right hemispheres (Profant et al. 2020). It is assumed that parallel changes in neuronal morphology accompany the reduction of the neuropil in each area.

Moreover, developmental changes in cortical volume vary by sex (Raznahan et al. 2011). The cortical surface area, which reflects complex interactions between brain size-related changes in cortical surface (or convex hull area), the degree of cortical sulcation (calculated as a gyrification index), and the area of cortex hidden in sulci may be adjusted in our species (Raznahan et al. 2011). Brain volumes can be larger in women in the prefrontal and medial paralimbic cortices (precentral gyrus, frontoorbital cortex, superior frontal, and lingual gyri), whereas large volumes in the medial and frontomedial cortex, angular gyrus, amygdala, and hypothalamus can be found in men (Goldstein et al. 2001; Kolb and Whishaw 2021). Interestingly, when assessed with near-infrared spectroscopy, the human prefrontal cortex responds to social/emotional facial expressions and shows sex differences for stimulus-induced selective activation of the cardiac activity (Fogazzi et al. 2020). Males and females respond differently to happy, disgusted, and fearful facial expressions, and higher sympathetic and lower parasympathetic activity occurred in young women when consciously and unconsciously processing negative emotions (Fogazzi et al. 2020).

9.3.1 Human Dendritic Spines Change from Prenatal to Elderly

The development, extension, pruning, and remodeling of human dendrites and spines occur prenatally and postnatally (see details in normal and pathological conditions below and illustrations in Fig. 9.25 in this chapter). Dendritic spines are absent or exist at very low density when cortical pyramidal neurons are developing

development and ADHD is a novel hypothesis that will guide both research and treatment for the foreseeable future" (Kolb and Whishaw 2021). It is also open to determine the role of dendritic spines in this condition.

in the human fetus, while the spine number increases and spine shapes change gradually along the final of the gestational period and after birth (Feldman 1984 and references therein). When differentiating into this specific neuron type, pyramidal cells begin the process of growing dendrites and the axon to establish synapses with other cells; dendrites emerge as simple processes and then ramify, and dendritic branches begin to form spines (Cajal 1909–1911; Kolb and Whishaw 2021).

Morphological data unraveled the gradual development of cortical spines in the human brain. The period of pyramidal dendritic differentiation and development in the visual cortex of the human fetus occurs between the 6th and 8th month of gestational age, which is relatively late when compared to the motor cortex (Feldman 1984). Distinct sequences of cortical ontogenesis follow the arrival of different afferent fibers to the developing cerebral cortex. The integration of incoming fibers and local cellular connectivity induces the formation and organization of the cortical layers and the development and maturation of cortical efferent neurons (Marín-Padilla 1970; see the pattern and distribution of axons around the cell body and proximal dendrites of developing pyramidal cells in Marín-Padilla 1974). Pyramidal cells show initially only a rudimentary smooth apical dendritic shaft, although the visual cortex can present visually evoked potentials at this stage (Purpura 1975b; Feldman 1984). At the 8th month, developing Meynert cells show lengthened apical dendrites, various basal dendritic sprouts, and abundant dendritic spines (Purpura 1975b; Feldman 1984). At this point, human spines are a "long, thin process, often with conspicuous varicosities (whose) trajectory may display prominent kinks or bends" (Feldman 1984). In the motor cortex, a small number of such thin processes can be observed as early as the 5th month, mushroom and stubby spines will appear later, but long thin spines still predominate (see additional data in Chap. 4 in this book).

Spines are evident in supragranular pyramidal and bitufted neurons of the precentral gyrus in a 1-month-old human infant (Cajal 1909–1911). However, the development of mature types of short spines will advance into postnatal life (Purpura 1975a, b; Feldman 1984; see also the postnatal development of spines in layer III pyramidal neurons in the monkey prefrontal cortex in Anderson et al. 1995). The dendritic fields of pyramidal neurons display progressively more branches and gradually occupy more space in the neuropil of the human cerebral cortex. This finding occurs around Broca's area at about 2 years of age, a finding that parallels the development of language in our species (Lenneberg 1967; Kolb and Whishaw 2021; see also the cytoarchitectural features of the orbital and frontal inferior gyri in a 6-year-old child in Fig. 4 from DeFelipe 2011). During childhood and puberty, there is an overproduction of dendritic spines in the human prefrontal cortex, remaining high until the third decade and reducing afterward (Petanjek et al. 2008; Sedmak et al. 2018). In adulthood, there are more spines at intermediate distances between proximal and most distal branches in both apical and basal dendrites of layer III pyramidal neurons of the adult cingulate cortex (Benavides-Piccione et al. 2013). No systematic variation in spine morphologies is evident along the dendritic distance from the soma (Benavides-Piccione et al. 2013). Furthermore, adult human pyramidal neurons may depart from the general description that proximal dendritic

segments are spine-free areas, showing spines distributed even at proximal primary shafts (e.g., along the initial 50 μm from the soma; Luengo-Sanchez et al. 2018; Rasia-Filho et al. 2021; see also the presence of these spines in pyramidal-like neurons below).

Throughout the human lifespan, neocortical areas show age effects on dendrites and spines in a nonuniform manner. Importantly, impairments in the complexity of spiny dendrite arborization, dendritic length, and spine numbers during normal aging and in neurodegenerative diseases can occur due to distinct mechanisms (Dickstein et al. 2007; see also a recent review by Aguilar-Hernández et al. 2023). Some spiny neurons may be well preserved in aged (>80 years) persons with adequate cognitive performance (Buell and Coleman 1981; Gefen et al. 2018). For example, Golgi-impregnated layer II pyramidal neurons from the parahippocampal gyrus (between the occipitotemporal sulcus and the apex of the gyrus) were studied in adults (mean age 51 years) and normal-aged individuals (mean age 79), and both were compared to patients with senile dementia (SD, mean age 76; Buell and Coleman 1981). Differences among the studied groups were found in apical and basal dendrites. Normal-aged individuals showed longer apical and basal dendrites and more branched apical dendrites. The greatest differences between groups were seen in the apical trees' terminal segments at distances intermediate from the soma, rather than at the proximal or distal extremes of the dendritic tree. Shrunken and atrophic dendritic trees were found in all cases (more in SD ones). These data indicate that the normal aging cortex contains regressing and dying neurons although surviving and growing neurons predominate normally (Buell and Coleman 1981).

Of individuals aged 69–102 years, six out of nine of them with clinical signs of senile deterioration, hippocampal pyramidal neurons and dentate gyrus granule cells showed changes correlated more clearly with the degree of antecedent psychomotor pathology than with chronologic age (Scheibel et al. 1976). Accordingly, in both cell types, spine loss followed a progressive if patchy course, peripheral dendritic segments usually denuded first, and basal dendritic shafts were affected before the degeneration was found in the apical shaft. Another scenario was found in the adjacent entorhinal cortex. In patients with age of 91, 92, and 102 years with mild-to-moderate emotional and intellectual changes, there was a relative persistence of a relatively high number of dendritic spines in pyramidal neurons until late in a degenerative fragmentation of the apical shaft (Scheibel et al. 1976).

In the human neocortex, basal dendrites of supragranular pyramidal cells were studied in the superior temporal gyrus (Wernicke's area) of both hemispheres and from men and women (18–79 years; Jacobs and Scheibel 1993). Data showed an age-related decrease in total dendritic length making that the interhemispheric dendritic asymmetries (greater values in the left hemisphere) were no longer significant in individuals over 50 years of age (Jacobs and Scheibel 1993). Data were also obtained from Golgi-impregnated neurons in the left prefrontal (supramodal frontopolar region, BA 10) and occipital (visual association region, BA 18) cortex. Regional differences and age-related changes in the spine density of basal dendrites of supragranular (most in upper layer III) small- to medium-sized pyramidal neurons were studied in neurologically normal individuals ranging from 14 to 106 years

old (Jacobs et al. 1997). Total dendritic length and dendritic spine number (summing all spines on dendritic segments) were higher in BA 10 than in BA 18. Dendritic spine density was greater in distal over proximal segments. A decrease of approximately 10% in total dendritic length values with age was found in both areas. There was a marked age-related decrease in dendritic spine density. Values showed a higher decrease until the 4th decade, providing an average of 46% fewer spines in both cortical areas from the younger group to the older group (Jacobs et al. 1997; Fig. 9.5). Aging also relates to dendritic atrophy, which starts approximately at 50 years of age, and loss of synapses in the posterior superior temporal gyrus (Anderson and Rutledge 1996). In this area, age was also negatively correlated with the number of primary basal dendrites, the total number of dendritic endings/branches, the total dendritic length, and the number of spines in supragranular pyramidal neurons in men from 21 to 71 years (Anderson and Rutledge 1996).

Likewise, data obtained from over 8,900 3D reconstructed spines along 6.35 mm of main apical and basal dendrites of layer III pyramidal neurons in the cingulate cortex (BA 24) showed differences when compared two men aged 40 and 85 (Benavides-Piccione et al. 2013). Spine density was higher in apical dendrites than basal dendrites in both cases. However, in the older individual, basal dendritic spine density (at approximately 70–130 μm from the soma) was significantly lower than in the middle-aged individual, with the density increasing to 1.2–1.3 spines/μm near 90 μm and remaining similar along intermediate to distal dendritic length. In the middle-aged individual, dendritic spine density increased to a maximum of nearly 1.8 spines/μm at 110 μm and slightly decreased along the remaining length of the basal dendrite. In apical dendrites of the middle-aged person, spine density slightly increased to a maximum of 4.3 spines/μm, whereas values were 2.2 spines/μm (both at 160 μm) in the older person (Benavides-Piccione et al. 2013). Apical dendrites from an individual at 40 years had longer spines than those in basal dendrites, a finding not found at 85 years. Moreover, a significant reduction in spine densities was found for the aged individual, with a loss of small and short spines in basal dendrites and long spines in apical dendrites (Benavides-Piccione et al. 2013).

In the human motor cortex of 14- to 96-year-old individuals, basal dendrites of both layers III and V pyramidal neurons decreased in number with advanced age, with marked differences between old and young groups in the deeper layer (Nakamura et al. 1985). Apical dendrites of layer III pyramidal cells in the human motor cortex show an age-related loss of spines (Watanabe 1981). In addition, in patients aged 74–102 years, layer V giant pyramidal neurons (Betz cells) of the motor cortex show aging and senescence changes represented by progressive loss of dendrite spines and shortening, disruption, and progressive disappearance of the normal long and circumferentially branched basal dendrites (Scheibel et al. 1977). From seven patients studied (three of them reported having mild or moderate senile changes), 75% or more of Betz neurons showed alterations by the eighth decade of life compared to less than 30% of the more numerous surrounding non-Betz pyramidal cells (Scheibel et al. 1977). These data would be related to motor impairments related to aging in humans. Comparatively, in the primary motor cortex of aged mice, apical

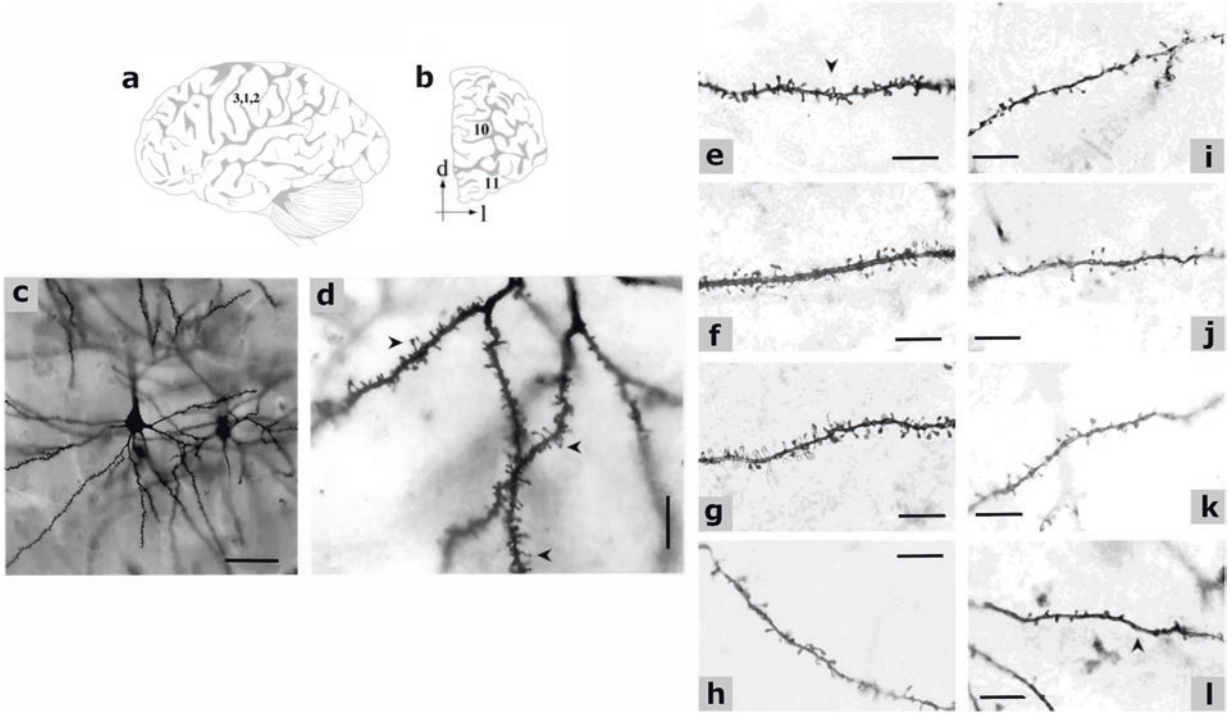

Fig. 9.5 (**a**) Lateral and (**b**) frontal views of the human left hemisphere illustrating the relative position of Brodmann's areas (BA) 3, 1, and 2 considered "low-integration regions" (in **a**), and BA10 and 11 classified as "high-integration region" (in **b**). d dorsal, l lateral. (**c**) Photomicrograph of Golgi-impregnated supragranular pyramidal neurons from the BA11 and (**d**) from BA 3-1-2. Note the varied number of spines with different shapes and sizes along the dendritic length, some with long and thin forms (arrowheads in (**d**)). Images (**c**, **d**) are from an 11-year-old child. Scale bar = 50 μm in (**c**) and 10 μm in (**d**). (Legends adapted and figures reprinted from Jacobs et al. (2001) under CCC RightsLink® license #5384350157140, originally published by Oxford University Press). (**e**–**l**) Photomicrographs of dendritic spines from the BA10 of four subjects younger than 50 years of age [14-year-old male (**e**), 23-year-old male (**f**), 32-year-old female (**g**), and 48-year-old female (**h**)] and four subjects older than 50 years of age [56-year-old male (**i**), 73-year-old male (**j**), 81-year-old female (**k**), and 106-year-old female (**l**)]. Note the general decrease in dendritic spines with increasing age (arrowheads in (**e**) and (**l**)). Scale bar = 10 μm. (Legends adapted and figures reprinted from Jacobs et al. (1997) under CCC RightsLink® license #5384350780357, originally published by John Wiley & Sons, Inc)

dendrites of layer V pyramidal neurons may be in a continuous state of instability and attempts at compensation, exhibiting an increased spine number with elevated turnover, short-term stabilization, and decreased survival (Davidson et al. 2020).

It remains to be determined if similar processes found in mice also occur in the motor cortex and associated areas in our species. If so, it will be important to identify at which point the net result of spine formation and removal tends to be a progressive age-related reduction in spine density affecting motor abilities, executive functions, cognitive performance, and social behavior display. To probe causal relationships is still challenging in humans because multi-faceted spine functions depend on the neuronal subpopulations, intraspine subcellular molecular and structural composition, and the multiple synaptic demands in different networks with short- or long-term demands, stability, or ongoing activity-dependent plasticity. Notably, pyramidal neurons show a reduction in dendritic length and complexity with additional changes in spine number, shape, and size along the human lifespan. The ontogenetic, morphological, and functional impact of these dendritic spines' changes on their corresponding synaptic sites can vary and be site-specific. For example, brain structural and functional impairments in aged individuals would relate to various behavioral deficits even in those persons with no neurodegenerative diseases; at the same time, some cognitive and emotional regulation would remain intact (Bagarinao et al. 2019 and references therein).

For emotional processing, subcortical and cortical regions crucial for the flow of information transfer among different functional brain networks ("connector hubs") would be affected by aging (Di Lorenzo Alho et al. 2016; Bagarinao et al. 2020). Age-related changes would alter the brain's intrinsic connectivity and overall connection strength for the whole-brain, short-range, and long-range connections (Bagarinao et al. 2020). Hub regions negatively associated with age include the following: (1) the medial precentral/midcingulate gyri and insula for both short-range and long-range connections' strength, and (2) the angular, middle frontal, and posterior cingulate gyri for long-range connections´ strength. Increases in whole-brain connectivity with age were found in the caudate, thalamus, cerebellum, hippocampus, and temporal pole (Bagarinao et al. 2020). These areas, which are also part of multiple large-scale brain networks (e.g., related to default mode, primary processing, visuospatial, salience, and executive control) are relevant for healthy aging and may be impaired in neurodegenerative diseases that cause progressive deficits in integrated brain functions.

Aging can alter the connectivity of the brain (Bassignana et al. 2022) and, possibly, the cortical neuropil structure and the spines' participation in synaptic transmission within circuits. Nevertheless, the pattern and impact of age-related reorganization of large-scale functional networks would account for individual variability in general cognitive performance (Bagarinao et al. 2019). It is currently open to be determined whether the remodeling of dendritic geometry, spine morphology, and connectivity would serve as a kind of adaptive response to progressive aging

effects in humans (Walker and Herskowitz 2021). These structural changes might compensate, within certain possible degrees and considerable interindividual variation, the "wear and tear" burden on the rate of brain aging upon network and neuronal functioning (McEwen 2007; Gefen et al. 2018; Rasia-Filho et al. 2018; WHO 2022).

In this regard, recent functional magnetic resonance imaging (fMRI) and multilevel data analyses from healthy adult men and women (from 21 to 86 years) helped to examine different spatial and functional organization of large-scale resting state networks in the human brain across the lifespan (Bagarinao et al. 2019). Results showed that (1) all canonical resting state networks, except the left and right executive control and dorsal default mode networks, negatively correlated with age; (2) aging relates to weaker within-network and higher between-network connectivity, indicating the reorganization of functional patterns toward more integrated network topology and increased global efficiency;[10] (3) the integrity of primary processing networks including visual and (lateral) sensorimotor networks, as well as the visuospatial network, would contribute to normal cognitive performance; and (4) connectivity among higher-level cognitive networks (including executive control, salience, basal ganglia, and dorsal default mode networks) was minimally affected by age-related connectivity alterations, which would be also relevant for individuals preserving general cognitive performance during healthy aging (Bagarinao et al. 2019).

9.4 Dendritic Spines in Human Cortical and Subcortical Areas Show Heterogeneous Morphological Features

Human cortical neurons are neither simply scaled-up versions of mammalian neurons nor generalizable building blocks of cortical networks between mammals (Mohan et al. 2015; Luebke 2017; Beaulieu-Laroche et al. 2021; Schmidt and Polleux 2022). Multiple evolutionary changes would have increased the number of neurons in the mammalian cerebral cortex and affected the average neuronal cell size and further elaborations of the dendritic and axonal arborization (Herculano-Houzel et al. 2014; Herculano-Houzel 2019). The specialization of our cortical circuits appears to be critical for our higher or more abstract mental abilities (DeFelipe 2011). This is a process involving a genetic background, a subcellular molecular and cellular structural and functional organization associated with learning-related plasticity, and network improvements (Nakahata and Yasuda 2018; Schmidt and Polleux 2022). Hence, neuron morphology relates to connectivity and synaptic patterns with nonrandom wiring in the cerebral cortex (Udvary et al. 2022).

[10] "Topologically direct interconnections between spatially remote brain regions will increase the efficiency of information processing, which is expected to yield benefits in terms of adaptive behavior. Brain networks can therefore be said to negotiate an economical trade-off between minimizing physical connection cost and maximizing topological value" (Bullmore and Sporns 2012).

It has been difficult to synthesize a large number of details into principles for understanding the brain (Leopold et al. 2019). Indeed, recent approaches evidenced the complexity of a connectomic study obtained from a rapidly preserved human surgical fragment of the temporal cortex (1 mm^3) imaged using a high-speed multibeam scanning electron microscopy (EM) and 3D image reconstruction (Shapson-Coe et al. 2021). This petascale connectomics dataset contained 57,216 cells and nearly 133 million synapses in a 1.4-petabyte volume. Most frequently, there were excitatory spiny neurons (69% of the neuronal population), excitatory synapses (76%), and the synaptic drive onto spiny neurons was excitatory (70%; Shapson-Coe et al. 2021). In another study using a realist model and rodent data, dense digital reconstruction of a 0.3 mm^3 cortical circuit exhibited approximately 31,000 neurons of 55 morphological cell types and 37 million excitatory and inhibitory synapses (Gal et al. 2021). Note the number of spiny neurons and the amount of synapses existing in a cortical minuscule portion (see also the discussion on how to analyze these complex data in Kasthuri et al. (2015)), which needs to be considered when developing computational models of human circuits function.

Not all human neurons show dendritic spines, as will be described below (Braak and Braak 1984a, b, 1986). On the other hand, spiny neurons are described throughout the human CNS,[11] from the spinal cord to high-order cortical areas. Morphological heterogeneity within each neuron type may exist for the dendritic branching pattern and spine density. Nevertheless, dendritic spines are usually in a *continuum* of shapes and sizes in these neurons. Pleomorphic (i.e., with different forms) spines may vary in number and distribution along dendritic segments in the same neuron. Considering the particular connectivity of each area, both neighbor and relatively distant spines have a crucial function in the synaptic establishment and information processing relevant to each local microcircuit and to large networks (Chen et al. 2011; Rochefort and Konnerth 2012; Kasthuri et al. 2015).

Jacobs et al. (2001) provided examples of the likely relationship between neuronal morphology and information processing. These authors studied Golgi-impregnated basal dendrites and spines of supragranular pyramidal cells in the left primary cortex (somatosensory, BA3-1-2; motor, BA4), unimodal cortex (Wernicke's area, BA22; Broca's area, BA44), heteromodal cortex (supplementary motor area, BA6β; angular gyrus, BA39), and supramodal cortex (superior frontopolar zone, BA10; inferior frontopolar zone, BA11). Primary and unimodal areas were

[11] There are open questions about the density and types of dendritic spines - if they indeed exist - in the morphologically heterogeneous populations of enteric neurons in our species. While submucosal neurons can be nondendritic, myenteric cells display around 20 very short dendrites arising from the cell body. These neurons were named Dogiel "spiny" (or with a "thorny" aspect) type I neurons. Considering the axonal and dendritic shapes, other Dogiel types I neurons were classified as "stubby," with short and partly stubby or partly lamellar dendrites, or "hairy" cells, with short and very thin dendrites. Dogiel type II neurons can show up to 16 dendrites, but these processes "look like" and behave as axons conducting APs. Types III and IV neurons are long dendritic, uniaxonal neurons. Type V neurons appear as unipolar cells with a single stem process projecting from the cell body. From this primary shaft, the single axon and various long, branched, tapering dendrites emerge (Brehmer 2021).

considered "low-integrative regions," whereas heteromodal and supramodal areas were "high-integrative regions." Morphological parameters evaluated were total dendritic length, mean segment length, dendritic segment count, and dendritic spine number and density. Even with interindividual variation, data from regions related to early stages of cortical sensory processing (primary cortex) and unimodal ones were consistently less complex than in those regions involved in the later stages of information processing (heteromodal and supramodal ones). In other words, total dendritic length and dendritic spine number in BA10 were greater than that in BA3-1-2 (31% and 69%, respectively), which indicates a broader sampling of afferent information upon dendrites and spines in the higher-order prefrontal area (Jacobs et al. 2001). A large dendritic arbor would enable further processing and provide more associative and learning properties. For example, in the monkey frontal eye field, the need to integrate large numbers of inputs for purposeful eye movements relate to basal dendrites of layer III pyramidal neurons. These neurons show the most complex branching pattern in the visual cortex and nearly 30% more dendritic spines than cellular counterparts in the parietal eye field areas (Elston and Rosa 1998).

Moreover, the basal dendrites of supragranular pyramidal neurons from the left human anterior insular gyri (the secondary gyrus brevis and the precentral gyrus) and posterior insular gyrus (the postcentral gyrus) revealed a specialized structural organization for this type of heteromodal cortex (Anderson et al. 2009). The insular cortex contains transitional zones from agranular–granular cytoarchitectonics, that is, from primitive allocortex to full-fledged isocortex along its anteroposterior extension. These insular portions have extensive interconnections with multisensory cortices, limbic structures (including amygdaloid nuclei), hypothalamic and brainstem nuclei to integrate multimodal interoceptive, emotional processing, and visceral reactions and to elaborate a "sense of self by relating the internal milieu with the external world" (Anderson et al. 2009 and references therein; see also Mesulam and Mufson 1982; Wattendorf et al. 2016). Interestingly, the human insular secondary gyrus brevis was more complex in terms of total dendritic length, dendritic segment count, and high dendritic spine number than either the precentral or postcentral insular gyri (Anderson et al. 2009). Compared to other neocortical areas, insular total dendritic length value was less than those found in heteromodal and supramodal "high-integration" areas (BA 6β, 10, 11, and 39), but greater than those in primary and unimodal "low-integration" areas (BA 3-1-2, 4, 22, and 44). The insular dendritic spine number was higher than both low- and high-integration regions. Greater values were found in the secondary gyrus brevis compared to both low and high-integration regions, whereas the precentral and postcentral insular gyri had more spines than the low-integration regions and similar values compared to the high-integration regions. Therefore, along with its anteroposterior and connectional organization, insular pyramidal cells may be a type of supragranular neuron with shorter dendrites provided with more spines to process convergent heteromodal stimuli (Anderson et al. 2009). It is important to consider that insular neurons can have particular synaptic integration strategies for very complex stimuli in our species (Anderson et al. 2009; Wattendorf et al. 2016; see also Khan et al.

2023). The emergent properties and synaptic processing executed by these circuits, synapses, spines, and dendrites may be one of our most complex. For example, the human insula is strongly activated when "you see the person you are in love with, try to listen to your own heartbeat, suffer from a headache, or crave for a chocolate cookie" (Gogolla 2017).

9.4.1 Multiple Possibilities for Modulation of Human Dendritic Spines

There are complex issues and implications for the study of brain areas and functions in humans. Due to clear ethical and technical reasons, we do not have the same amount of information about human dendritic spines as currently available from other species. Some reports on humans were also limited to the number of cases and kind of samples studied. However, descriptive morphological data constitute the foundation for further understanding of the nature of the human brain, its cellular and circuitry´s functional organization for the display of complex behaviors (DeFelipe 2022). This kind of knowledge forms the basis for further progress on neuroanatomy with a potential clinical implication. They can also be linked with precise imaging techniques and current genetics approaches (Grasby et al. 2020; Yuste et al. 2020; Kiwitz et al. 2022).[12]

From technical reasons to marked neuroanatomical differences in development and ultimate identification of borders, some areas impose more difficulties than others do for their study in humans. For example, evident phylogenetic discrepancies

[12] Important current data are available from the following sources: (1) cellular-resolution atlases of the human brain (e.g., Ding et al. 2016; Mai et al. 2016); (2) human brain anatomy using modified Brodmann or gyral annotation and gene expression data in 3D images (Allen Brain Atlas, https://human.brain-map.org/static/brainexplorer; https://atlas.brainmap.org/atlas?atlas=265297126#atlas=265297126&plate=112360888&structure=10390&x=40320&y=46976&zoom=-7&resolution=124.49&z=3; and, https://atlas.brainmap.org/atlas?atlas=138322605#atlas=138322605&plate=112360888&structure=10390&x=40320&y=46976&zoom=-7&resolution=124.49&z=3); (3) atlas of transcriptional features of the mid-gestational human brain (Miller et al. 2014); (4) segmentation of volumetric brain MRIs of infants (first 2 years of life; de Macedo Rodrigues et al. 2015); (5) connectomic study of adult human cerebral cortex on a petascale fragment (e.g., Shapson-Coe et al. 2021; available to peruse online and accessible with the Neuroglancer browser interface); (6) multimodal cell census and atlas of the mammalian primary motor cortex, including human data, and integrating neuronal multi-layered molecular genetic and spatial information with multi-faceted phenotypic properties (BRAIN Initiative Cell Census Network (BICCN) 2021); (7) the "BigBrain" model based on human cell body-stained and 3D-reconstructed sections as an anatomical brain model at a spatial resolution of 20 μm to be associated with ultra-highfield fMRI (with "possibility to measure laminar brain activity as well as identifying functional subdivisions of subcortical and cortical structures"; Kiwitz et al. (2022), and references therein; see also https://interactive-viewer.apps.hbp.eu/, https://ebrains.eu/, and https://ebrains.eu/service/voluba/); and (8) the methodological approach for studying synaptic and non-synaptic profiles of nearby axons and dendritic spines in Kasthuri et al. (2015), for example.

exist for the human hypothalamus and its subdivisions (Saper 2012).[13] Let us also consider the following:

1. It may be more difficult to discern a clear relationship between structure and function in cortical associative areas (Scheibel et al. 1990). That is because there can be a large degree of interindividual variation in dendritic structure complexity in these areas. It is important to have extensive information about the life history, the nature of the work and other social activities, and personal abilities of individuals to describe who serve as subjects for this type of study (Scheibel et al. 1990; Jacobs et al. 1993; see how the functional architecture of the brain is modulated by literacy in Petersson et al. 2001). In addition, there are functionally phenotypic subtypes of pyramidal neurons within cortical layers (Berg et al. 2021; Moradi Chameh et al. 2021; Planert et al. 2021) not detected by histological techniques. Other locally non-spiny neuronal types coexist intermingled with pyramidal cells and do modulate large network inputs and local microcircuitries, influencing selectively dendrites and spines across cortical layers (Kubota et al. 2007, 2016).[14]
2. Cortical areas are currently recognized as a "mosaic" with higher interconnectional complexity, functional networks, and multiple cortical finer-grained parcellations than previously thought (Glasser et al. 2016; Kolb and Whishaw 2021). The neuronal structure is influenced by both local and extrinsic connectivity, and then, the connectional strength is very likely affected and can be reciprocally affected by the dendritic geometry (length, diameter, and branching pattern) associated with all dendritic spine morphological and functional features. Rather than a simple junction of one cortical module with another, there can be a dynamic interplay with feedback and feedforward loops between and among the operation of different subcortical and cortical regions (Kolb and Whishaw 2021). This kind of network organization suggests that the topography of a cortical area and specific functions can be variable between individuals at the same time that subpopulations of neurons with different features can be intermingled within the same area (Anderson and Rutledge 1996). For instance, the face area of the motor cortex also contains neurons that innervate the adrenal

[13] Immunohistochemical characterization of hypothalamic neurons and description of species differences in neuroanatomical subdivisions can be found in Saper (2012). Examples of Golgi-impregnated spiny neurons in hypothalamic nuclei obtained from other species were depicted by Cajal (1909–1911), and the history of neuroendocrinology since the descriptions in *De humanis corporis fabrica* by Vesalius can be found in Kreier and Swaab (2021). See data on pituitary alterations in humans in Baltazar-Gaytan et al. (2019).

[14] For example, horizontal cells in layers I and II, double bouquet cells in layers II and III, chandelier and neurogliaform cells in layers II to IV, basket cells in layers III and IV, spiny stellate cells in layer II and aspiny stellate cells in layer IV, Martinotti cells in layer VI, fusiform stellate cells in layer VI, and a varied group of pleomorphic neurons identified as "modified pyramidal cells" in layer VI, among other varieties of non-spiny or sparsely spinous non-pyramidal heterogeneous cells found in the cerebral cortex of various species (see further data in Lodato and Arlotta (2015) and Kubota et al. (2016) for the complexity of these local cells; and, in addition, Braak 1980; Feldman 1984; Wahle 1993; Pearson 1995; Rudy et al. 2011; Leopold et al. 2019).

medulla, which may modulate sympathetic responses elicited in concert with facial emotions (Leopold et al. 2019).

Subtle but distinct neural processing may coexist in the same area. Cortical responses with laminar synaptic elaboration and cellular functioning differ if a hand movement is executed or just imagined (Persichetti et al. 2020)[15]. In this regard, the precentral cortical gyrus contains multiple and partially overlapping sites whose activation occurs for the motor programming of the wrist and single finger movements (Matelli et al. 2004). Cortical cellular modules coexist side-by-side in the human primary motor cortex (M1; Persichetti et al. 2020), and approximately one million axons in each pyramid compose the corticospinal tract in humans (Schoenen and Grant 2004). By testing the responses of the identified human hand-selective region in the M1, executed movements of finger tapping enhanced activity in both the superficial layers (II-III), which receive cortico-cortical input, and the deep layers (Vb-VI) that send output to the spinal cord. When the task was imagining the movement, a laminar-specific evoked response remained restricted to the superficial circuitry of adult individuals (Persichetti et al. 2020). These neuroanatomical and functional data relate not only to extrinsic and intrinsic cortical circuitries but also to plastic and learning effects for neural repetition improvements (i.e., repetition priming) in behavior (Persichetti et al. 2020). Second, in sexually active women (aged 18–45 years), the somatotopically ordered representation of the female clitoris lies in BAs 1, 2, and 3a/3b, dorsolateral in the postcentral gyrus (S1) adjacent to the representation of the hips and upper legs, and not in the mesial wall of the precentral lobe as hitherto considered (Knop et al. 2022). Individual variability of the precise location of the clitoral region, and sensory-tactile stimulation of the clitoral region evoked bilateral neural activations in S1 in most women or, in some cases, activation in either the right or the left hemisphere only. Structural plasticity findings involving local connectivity showed a positive correlation between the cortical thickness of the individually mapped left-hemispheric genital field and the frequency of sexual intercourse within the past 12 months (Knop et al. 2022).

3. The dendroarchitecture and the functional dendritic domains are associated with spine computations for synaptic processing and integration. A higher number of spines in dendrites imply many forms of synaptic establishment and modulation, long-term neuronal plasticity, learning, and memory, varied biochemical cascades, and molecular interactions modulated by the synaptic demands (Yuste 2010; Sala and Segal 2014; Nakahata and Yasuda 2018). Interestingly, differences between the left and right hemispheres exist for morphological features of human cortical neurons. For example, in seven out of nine subjects, supragranular pyramidal neurons of the posterior superior temporal gyrus posterior to Heschl's gyrus showed longer dendrites, more dendritic branch endings, and

[15] See also data on human cortical stimulus-related hemodynamic changes and the modulation made by task difficulty, arousal, and behavioral performance in Oelschlägel et al. (2022) and Burlingham et al. (2022), respectively. Commentaries on results from alert-behaving monkeys can be found in Sirotin and Das (2009) further discussed in Leopold (2009).

more dendritic spines in the right hemisphere than in the left hemisphere, where it corresponds to Wernicke's area (Anderson and Rutledge 1996).

4. There may also exist differences between males and females in dendritic spine number in subcortical areas revealed by experimental and morphological data using rats (e.g., in the medial amygdaloid nucleus, Rasia-Filho et al. (2012) and references therein) or in human cortical neurons. For example, there was a significant interaction between sex and insular gyri for total dendritic length and dendritic spine number. Men showed supragranular pyramidal neurons longer and with more spines in basal dendrites than the corresponding area in women (Anderson et al. 2009). On the other hand, women exhibited slightly greater basal dendritic values and variability in supragranular pyramidal cells in Wernicke's area, related to language comprehension, than men (Jacobs et al. 1993).
5. Finally, it has to be considered that "snapshots" of dendritic spines number and shape likely represent a moment within a dynamic time window for spine formation, stabilization, persistence, or shrinkage (von Bohlen und Halbach 2009; Davidson et al. 2020; Kasai et al. 2021; see also the first chapter of this book). For different neuronal subpopulations or the morphological and functional heterogeneity within the same class of neurons, it is conceivable that subtle differences can exist *in vivo* and involve a variable proportion of intermingled, neighbor dendritic spines (Chen et al. 2011). These spines can be stable or plastic and their number, shape, and composition can adapt to physiological demands. Plastic dendritic spines can show functional selectivity and be sensitive to specific stimuli along the same segment, but spine structure–function couplings of such kind cannot be assessed with current techniques in humans.

We have not reached the ultimate interpretation of the morphological features of all nerve cells in the human CNS. Nevertheless, even considering various technical limitations, there are relevant reports reflecting decades of study of human spiny neurons and their likely integrated functions across CNS areas and functional circuits. Some examples of human neurons will be presented in the following sections with representative figures, maintaining the original description and classification of cells and spines. To be more concise, data on the axonal aspect of each neuron will be omitted most frequently. For additional data, the interested reader is directed to relevant morphological descriptions that can be found in the references indicated in the text.

9.4.2 Spinal Cord

Neurons showing many spines and others with few spines form part of different afferent and efferent pathways in the human spinal cord (Schoenen 1982a, b; Fig. 9.6). It is plausible to consider that neurons that possess more dendritic spines would modulate differently the axonal inputs they receive than those neurons whose

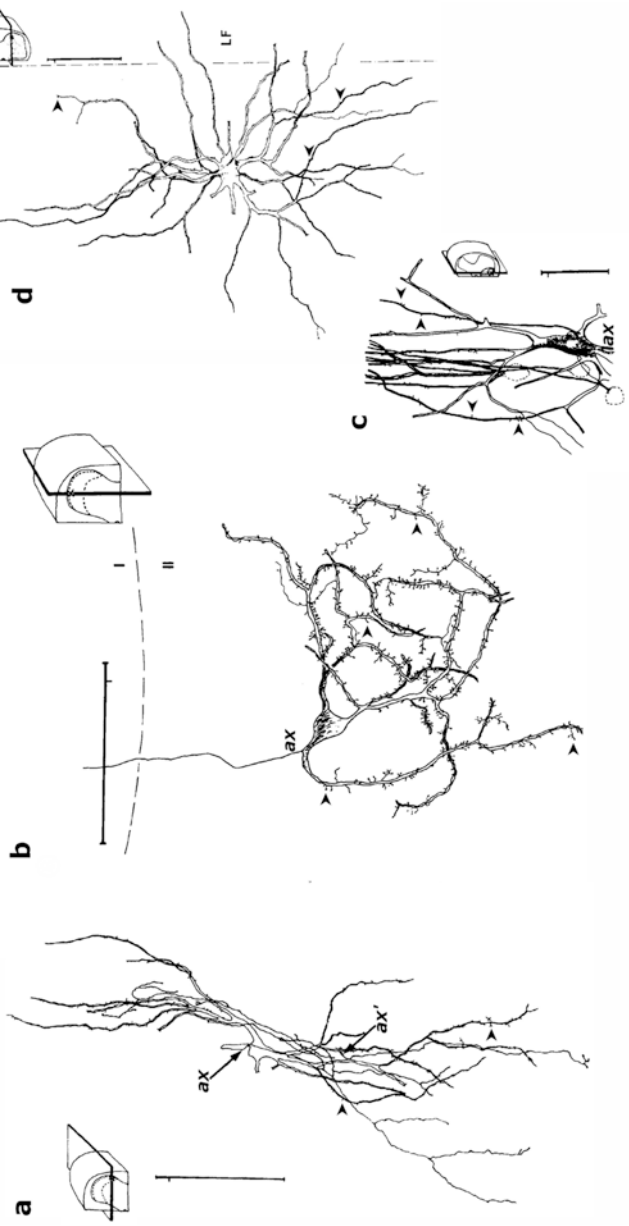

Fig. 9.6 Camera lucida drawings of Golgi-impregnated neurons from the human dorsal (**a**, **b**) and ventral (**c**, **d**) horns of the spinal cord. (**a**) Islet cell in lamina II in the cervical enlargement of a 2-month-old infant. This cell has two axons, one (*ax*) emerging from the perikaryon and another (*ax'*) from a secondary dendrite. Note the presence of a few spines (arrowheads) in this neuron and compare it to those more abundant in a (**b**) curly cell in the lamina II in the lumbar enlargement of a 1-day-old neonate. (**c**) Ventromedial motoneuron in the lumbar enlargement of a 2-year-old child. (**d**) Dorsolateral motoneuron in the lumbar enlargement of a 28-week-old fetus. The impregnation of dendritic spines (arrowheads) was variable in the studied samples. LF lateral funiculus. The plane of cutting where each neuron was observed is indicated by a scheme of the corresponding part of the spinal cord (drawn in perspective at the top of each image). Scale bar = 100 μm (one subdivision at 10 μm is shown). (Legends adapted and figures reprinted (**a**, **b**) from Schoenen (1982b) under CCC RightsLink® license #5384201195677, originally published by Elsevier; and (**c**, **d**) from Schoenen (1982a) under CCC RightsLink® license #5384330581077, originally published by John Wiley & Sons, Inc)

afferents make synapses directly upon spine-free dendritic shafts. Smooth dendritic segments are equally important for synaptic integration (Kubota et al. 2016), and, theoretically, the axodendritic contacts would transform fast and less modulated synaptic inputs into voltage changes in the target dendritic segment. On the other hand, axospiny synapses let the synaptic input more modulated and would balance inputs' strength and plasticity with more possibilities of information processing and integration. It is a counterintuitive possibility to be proved that some circuits need a more direct, rapid, and less modulated effect on dendrites and neuronal excitability, whereas others evoke responses integrating spines' processing for weighing the afferent pattern activity, intensity, and plasticity.

Considering the spinal cord physiology, local afferent pathways coding noxious stimulation can induce motor reflex and hemodynamic responses (Cravo et al. 1995). At the same time, plastic excitatory responses in postsynaptic targeted neurons in the dorsal horn can be induced by the intensity and chronicity of stimulation involving, the neurotransmitter, neuromodulator, and neurotrophic factor released (Basbaum 2021; Gardner 2021). In the ventral horn of the spinal cord, proper and fine-tuned muscle contraction and relaxation are orchestrated by different motoneurons, which accommodate, balance the impact, and compute several ongoing inputs from various central motor control areas (Scott and Kalaska 2021). The morphology of each neuron in the spinal cord reflects the circuitries' properties and synaptic modulation they compute and the cellular role in specific intrinsic or projecting pathways. This rationale applies to other brain areas and essentially reinforces that morphology and function are two sides of the same token, although it has to be demonstrated in detail in each studied area. Even though these concepts may appear obvious, the myriad of neuronal shapes and different circuitries in humans are not indeed.

For example, the morphology of Golgi-impregnated neurons in the human spinal cord was obtained during 26 weeks of gestational age, adult life, and into old age by Shoenen (1982a, b). The dorsal horn has neurons with distinct dendroarchitectonic and neurochemical features, dendrites with preferential orientation in one or more spatial planes, and varied spine densities. Dorsal horn neurons receive superficial, deep, and visceral somatosensory inputs from approximately 2–2.5 million fibers in human adult dorsal roots on each side (Schoenen and Grant 2004). Lamina I contains a uniform population of large, poorly ramified neurons with disk-shaped dendritic arbor and spiny branches projecting ventrally into the adjacent lamina II, some reaching layers III and IV or the white matter. These neurons are moderately covered with "sessile" or "pedicled" dendritic spines, more numerous on the ventral dendrites (Schoenen 1982b).

Four neuronal types compose the human lamina II (the *substantia gelatinosa*): (1) "Islet cells," which display a cylindrical "parasol pine" dendritic tree shape or primary dendrites on two opposite poles of the soma with sparse and irregularly distributed dendritic spines in small bunches (Fig. 9.6a); (2) "filamentous cells," small-sized neurons characterized by multiple filiform spiny dendrites (spines are more numerous on these filiform dendritic branches than on the thick ones); (3) "curly cells" with the most complex, twisted, spine-rich dendrites, and spines with

a thin stubby-necked aspect covering the entire dendritic tree, except the initial segments of primary dendrites (Fig. 9.6b); and (4) "stellate cells," which display a simple dendritic tree architecture and various primary straight dendrites (some curved and recurrent) with spine-poor branches extending into laminae I and III, or with branches covered by numerous spines on thin collateral branches, but also irregularly distributed over main shafts of the dendritic tree (Shoenen 1982b).

Lamina III shows a mixed population of "antenna-like cells" with an asymmetric dendritic tree, cone-shaped dendritic aspect, and numerous short-necked dendritic spines. Local "radiate cells" have a radial dendritic tree and spherical territory. Lamina IV neurons are medium- or large-sized "antenna-like cells" with an asymmetric dendritic tree, some reaching the neuropil of lamina II and I, and richly covered with dendritic spines on dorsal dendrites (Shoenen 1982b; see also Sengul and Watson 2012).

These dorsal spinal cord neurons relate to afferent, intrinsic, and efferent pathways. For example, lamina II neurons integrate segmental and suprasegmental influences in the modulation of nociceptive transmission (Sengul and Watson 2012), curly cells have an axon projection directly into lamina I, islet cells might be inhibitory interneurons in nociceptive processing, whereas stellate cells might integrate inputs to lamina II and transfer them to the deeper lamina III to V (Shoenen 1982b). Lamina I neurons receive inputs coming from peripheral nociceptors, which form multiple contacts with local dendrites, as well as other inputs from non-noxious mechanic stimuli. These neurons' axons and those from laminae IV and V compose the ascending sensory spinothalamic tract (Shoenen 1982b; Murray 1995; Schoenen and Grant 2004; Basbaum 2021).

Ventral motoneurons have a particular dendroarchitectonics and organization in columns developed for multiple connections and integrated functions (Shoenen 1982a). One somatic motoneuron, "the final common pathway" of Sherrington, receives the convergence of inputs of approximately 10,000 axon terminals from descending pathways of different sources (Murray 1995). Furthermore, although the motoneuron cell body can be localized into a specific ventral lamina, dendrites can extend into the intermediate zone and the dorsal horn as well as reach the white matter (Murray 1995). This structural organization relates to an enormous receptive field (see drawings of representative spiny neurons from various species in Cajal (1909–1911)). Other motoneurons are propriospinal interneurons, such as most lamina VIII neurons, and coordinate motor activity including long pathways that connect upper and lower spinal cord segments for forelimb and hindlimb movements (e.g., the reciprocal arm and leg swing in walking; Sengul and Watson 2012).

Four motor neuron columns were described in the human lumbar spinal cord (Shoenen 1982a). The ventromedial column motoneurons have one or two thick primary dendrites arising from the dorsal surface of the cell body forming tight bundles, and ventral primary dendrites that are more numerous (three to five), which ramify in a fanlike arrangement and display more spines (Fig. 9.6c). Vertical dendritic bundles are long and narrow-meshed, extending over 2–3 mm in the ventrodorsal axis. Longitudinal dendritic bundles are composed of branches of variable thicknesses and orders from neighboring neurons and from cells several hundred

micrometers distant from each other in the rostrocaudal axis. Motoneurons of the central column have a radial, multipolar dendritic tree predominantly oriented longitudinally and with sparse spines, whose primary to tertiary branches form large transverse bundles or thin longitudinal plexus. Ventrolateral column motoneurons present a radial dendritic tree. Most dendrites have a longitudinal orientation and form bundles, which also occur in the transverse plane, forming the largest dendritic domain rostrocaudally in the spinal cord. Motoneurons of the dorsolateral column display a rich multipolar dendritic tree, mostly branched out in the transverse plane and some forming small bundles of short dendrites that can extend into the white matter (Fig. 9.6d). Dendritic spines are scarce, although relatively more numerous on proximal dendrites than on distal branches (Shoenen 1982a).

These data indicate that motoneurons likely form most synapses directly on dendritic shafts to compute information from multiple descending motor pathways and propriospinal fibers. Integrated with their intrinsic membrane properties, the synaptic impact of different inputs along the dendritic length within specific time windows will determine the resultant firing pattern of these cells to control and execute phasic and tonic muscle contraction. This is a complex task. In macaques, M1 corticomotoneuronal (CM) cells project monosynaptically to spinal motor neurons and control a single hand muscle, although showing an extensive overlap of axonal branches with the distribution of other M1 neurons that control different hand muscles. Moreover, a single CM axon terminal arborizes extensively in the ventral horn of one or various segments of the spinal cord. The terminal ramifications form synapses with spinal cord motorneuron pools of different intrinsic hand muscles and with different combinations of spinal cord interneuronal networks, which can also activate different combinations of agonist and antagonist (flexor and extensor) muscles (Scott and Kalaska 2021 and references therein). In this example, spinal motoneuron dendrites with heterogeneous spines integrate programmed, learned, feedback, and feedforward synaptically mediated codes to display the fine control necessary for movements of the distal parts of the limbs (Sengul and Watson 2012; Scott and Kalaska 2021; see also the effects of electrical stimulation of dorsal roots C3 to T1 on the arm and hand motor control in two patients with chronic post-stroke hemiparesis in Powell et al. 2023).

9.4.3 Brainstem and Cerebellum

There are few morphological descriptions of human brainstem spiny neurons. Brainstem morphology, itself, is diverse reflecting its varied functions, neuroactive elements, and intrinsic neural pathways. The anatomical organization of the human brainstem is a complex combination of neuronal groups and cell areas with differing cytoarchitecture (Koutcherov et al. 2004; Paxinos et al. 2012; see also Ding et al. 2016). Descriptions and delineations of brainstem nuclei have been based on topography, cytoarchitecture using Nissl staining, myeloarchitecture, connectivity, and chemoarchitectonic analysis of reactivity patterns to acetylcholinesterase, tyrosine

hydroxylase, NADPH diaphorase, bombesin, substance P, and neuropeptide Y, among other histochemical markers (Koutcherov et al. 2004; Paxinos et al. 2012). Findings from other mammals (e.g., mice, rats, cats, dogs, and rabbits) are mentioned for comparative reasons and to provide some insights into expected human data.

Different types of neurons were found along the various brainstem areas, some with sparse spines (Cajal 1909–1911). For example, (1) the hypoglossal nucleus (XII cranial nerve) of the newborn mouse and cat presents large cell bodies with long, thick, winding, and typically spiny dendrites radiating in all directions, some ending within the nuclear borders and others extending outside to lie parallel or perpendicular to the fibers associated with the central pathway of the vagus and glossopharyngeal nerves; (2) the dorsal motor nucleus of the vagus nerve (DMV, X cranial nerve) of newborn cat contains relatively large motor neurons with short primary dendrites that give rise to branched segments, all covered with a moderate to a large density of spines (some spines also protruding from the cell body). These cells are intermingled with relatively small neurons with smooth or spine-poor dendritic segments and short axons, whereas other cells, similarly shaped, show a moderate to a large number of spines and axons grouped to form the motor root of the vagus nerve; in humans, the DMV is formed by two zones, one is superficial and showing more widely spaced cells, and another is deeper and show more densely packed cells; (3) neurons in the nucleus *ambiguus* of the cat medulla have thick dendrites classified with moderate density to "spine-laden" segments; (4) in the newborn mouse, neurons in the lateral vestibular nucleus of Deiters show stellate, multipolar cell body and long, spiny dendrites that divide repeatedly. In contrast, neurons in the vestibular ganglion show a fusiform cell body and two straight, predominantly smooth or spine-poor dendrites arising from opposite somatic poles; (5) in the ventral cochlear nucleus of a neonatal cat, fusiform cells display one or two short primary dendrites (some with more very short primary shafts), which are covered with numerous and pleomorphic spines in intermediate to distal shafts and branches (other shapes for spiny neurons are found in the dorsal cochlear nucleus); (6) in the cat and rabbit dorsal nucleus of the raphe, fusiform, triangular, or stellate neurons display very spiny dendrites (also found covering the cell body of some cells) extending along the dorsal to ventral transversal plane; and (7) the rabbit interpeduncular nucleus have neurons with an ovoid, fusiform, or triangular cell body and two to four thick primary shafts which branch sparingly and, after a rather long course, dendrites have a number of thick and short spines, occasionally ramifying as a bouquet of spiny tangled branches or two or three terminal branches (Cajal 1909–1911; Cajal 1995 translated from the original work).

The spatial orientation of dendrites and the distribution, number, and type of spines would be related to the local cellular packing density, neuroanatomical disposition of afferent pathways, and the role of each area in hierarchical or parallel circuits receiving axon terminals or "en passage" collateral fibers. Then, the dendroarchitecture and connectivity of these spiny neurons would suggest the existence of neuronal populations with different coding strategies for processing specific stimuli. Likewise, they would indicate whether the same neurons elaborate more than one

type of information by dealing with different spatiotemporal inputs computed along the dendritic tree. Again, the scenario can be complex. Ultrastructural data demonstrated that a single dendritic spine in the cochlear nuclei might receive nine axon terminals and form symmetric synapses containing vesicles of different sizes (and assumed different transmitter content) in the adult rat (Peters et al. 1991).

Moreover, the functional implication of basic neuroanatomical and molecular research of human brainstem nuclei can be highly significant by revealing the patterns of innervation and action upon target sites for the projections from the serotoninergic raphe nuclei, noradrenergic cells in the *locus coeruleus*, and dopaminergic neurons in the ventral tegmental area in the mesocorticolimbic circuitry, to cite a few examples (see also Paxinos et al. 2012; Benarroch 2018; Horn et al. 2020; Saper and Elmquist 2021).

Let us consider another example of an important integrative brainstem area, the nucleus of the solitary tract in the dorsal medulla (NTS; Paxinos et al. 2012; Zoccal et al. 2014; Holstein 2020; Saper and Elmquist 2021). Local neurons are functionally organized to receive inputs and participate in the baroreflex and chemoreflex control of blood pressure, respiratory function, wake-sleep cycle, integrated vestibular responses, esophageal-mediated vago-vagal gastric reflexes, taste perception, and activation of hypothalamic neuroendocrine secretion. In adult rats, NTS neurons receiving viscerosensory inputs and those that project to the DMV display morphologic characteristics correlated with the type of afferent synaptic information they process (Glatzer et al. 2003). Three types of local neurons were identified with one to six primary dendrites "relatively aspiny," that is, with scarce spines of different shapes, some protruding from the cell body and proximal dendrites (see Figs. 3D and 6 in Glatzer et al. 2003). "Group I" neurons have a small soma, three or fewer dendrites, and a relatively small proximal dendritic arbor; "Group II" neurons have a larger cell body area, four or more dendrites branching near the soma, and a larger dendritic arbor than group I neurons; and "Group III" neurons share some morphological similarities with Group II cells, except that they show longer primary dendrites and shafts branching further away from the soma (Glatzer et al. 2003).

Interestingly, there is a transient increase in the number of dendritic spines in NTS neurons of rats (Vincent and Tell 1999). At birth, there are no such "appendages," but the number of pleomorphic spines (some thin and long) covering secondary dendrites reaches a maximum at postnatal day 12 and decreases until adulthood to remain at a very low density (see Figs. 1 and 5 in Vincent and Tell 1999). These findings suggest a functional adjustments with dendritic segments adapting the number of spines and promoting synaptic stabilization in a gradual way. Moreover, contacts are rather made on smooth parts of the dendrites of NTS neurons. In adult hamsters, dendrites are sparsely to moderately covered with pedunculated, filiform, claw-shaped, small, thin pedunculated, and short, blunt spines along the extension and spatial orientation of branches in different neuronal subpopulations and NTS subdivisions (see Figs. 13 and 15 in Whitehead 1988). These morphological data have to be linked to the way NTS neurons are receiving information from multiple

sources and integrating different functional responses, which likely present some homology in humans (see further data in Ran et al. 2022).

Further morphological data may also shed light on the synaptic organization of other brainstem structures that elaborate sympathetic and parasympathetic homeostatic (and allostatic) responses, micturition, nociception, alertness, defensive and anxiety-like behaviors, vestibular, auditory, visual, and other sensory and motor cranial nerves functions. Various areas along the brainstem are also connected with subcortical/basal ganglia/cerebellar and cortical circuits to modulate positive and negative emotional expressions in our and other species (Calanchini et al. 2016; Leopold et al. 2019). Groups of cells in regions or defined nuclei and their pathways participate in motor control, including adjustments of spinal reflexes, muscle tone, posture, and voluntary movements (for Nissl-stained soma and primary dendrites of magnocellular red nucleus neurons in humans; see Onodera and Hicks 2009). These emotional and motor circuits provide more complex behavioral displays than those generated by neuronal ensembles near cranial nerves in the brainstem reticular formation called "pattern generators" for stereotyped innate responses (Saper and Elmquist 2021). Indeed, considering an evolutionary perspective, facial expressions are a relevant part of our social communication and social intelligence (Schmidt and Cohn 2001; see additional data on the amygdaloid function in this chapter). There is a complex descending cortical command to the brainstem motoneurons composing the facial nerve (VII cranial nerve) to control 17-paired mimetic facial muscles. The cortical motor control of facial expressions has a distributed neural representation in each brain hemisphere, involving the primary motor cortex, the ventral lateral premotor cortex, and the supplementary motor area on the medial wall for the voluntary control of facial expressions, and the rostral and caudal cingulate cortex to elaborate our emotional expressions (Müri 2016).[16]

The human mesencephalic periaqueductal gray (PAG) is part of the neural circuits activated by nociception and for analgesia (Basbaum 2021) as well as for basic emotions (grief, joy, rage, and fear—see Fig. 3 in Panksepp 2016) or maternal love (Zeki 2007). The PAG neurons are relevant components of the human capacity for speech, forming a species-specific circuit for our emotional expressions and vocalization (Holstege and Subramanian 2016).[17] It is connected with the superior

[16] "In humans, the motor nucleus of the facial nerve is the largest of all motor nuclei of the brainstem... The comparative anatomy of the facial musculature and of the central nervous apparatus that controls facial movements suggests that, in some primates, group size, facial motor control, and primary visual cortex evolved with the same pattern... Species living in relatively large social groups tend to have relatively large facial motor nuclei, and species with enlarged facial nuclei and facial mobility have rather large primary visual cortices... Great apes and humans have facial motor cortices that are thicker and richer in local circuitry, their facial movements have the highest degree of dependence on the primary motor cortex... (and) more pronounced direct cortico-facial projections" (Müri 2016 and references therein).

[17] As described by Holstege and Subramanian (2016), human speech needs the activation of two motor systems: one generates vocalization by activating the prefrontal - PAG - nucleus retroambiguus (NRA)–motoneuronal pathway, and the other modulates vocalization into words and sentences by activating the motor cortex and the corticobulbar fibers to specific muscles. The PAG has a central role in the "emotional motor system" when vocalizations also express emotions (e.g.,

colliculus and modulates aversion and defensive behaviors (Laemle 1979; Brandão et al. 1994; see additional functional implications in Carrive and Morgan 2012).

Golgi-impregnated PAG cells were studied in two men (28 and 45 years of age) and were classified as "fusiform" or "multipolar" neurons (Gioia et al. 1998). Fusiform neurons have two primary dendrites emerging at opposite somatic poles, which are straight and smooth but ramify to secondary spiny dendrites. Multipolar neurons have more primary dendrites branching in all directions and at variable lengths. These branches provide a radial aspect for the dendritic field. The primary dendrites are usually smooth, and the density of spines increases in dendrites of second or higher order. Multipolar neurons are the spiniest local ones, have an extensive receptive dendritic surface, and are classified as projection cells (Gioia et al. 1998). Additional morphological descriptions on dendrites and spines of Golgi-impregnated PAG neurons were obtained from fetuses to adult humans (Laemle 1979). In these samples, most neurons were small to medium-sized and were named (1) "vertical" cells with one or two (occasionally three) primary dendrites; (2) "stellate" cells with four or more randomly oriented primary dendrites and radial dendritic field; (3) "horizontal" cells show one or two primary dendrites, less spiny dendrites than the other local cells but with spines tending to be in clusters, and having a preferential mediolateral dendritic field; and (4) "other types," which display a triangular cell body resembling pyramidal and "inverted pyramidal" cells and three primary dendrites that ramify sparingly to generate spiny branches. Both densely and sparsely spinous cells were observed, and, notably, pleomorphic spines were found even in fetal tissue. Some dendrites crossed the midline and extended into the contralateral PAG or were directed to the superior colliculus. These data indicate that local cells have multiple receptive fields and process inputs even outside the PAG boundaries (Laemle 1979).

The human superior colliculus receives visual inputs and presumably orients the head and eyes toward salient stimuli in the environment (Tardif et al. 2005; Vanderah and Gould 2021). Five types of neurons were identified in its deep layers: (1) horizontal cells; (2) vertical cells; (3) pyramidal cells; (4) inverted pyramidal cells; and (5) stellate cells (Laemle 1983). In the superficial layers of the human superior colliculus, neurons were classified as (1) small marginal cells with a locally oriented dendritic field; (2) horizontal cells presumed to be interneurons; (3) piriform cells; (4) stellate cells with multiple radiating dendrites; (5) narrow field vertical cells, with dendrites vertically oriented and cylindrical fields; and (6) wide-field vertical cells, with dendrites extending obliquely toward the surface and forming a broad field (Laemle 1981; May 2006).

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crying and laughter in humans). "The PAG receives strong projections from higher limbic regions and from the anterior cingulate, insula, and orbitofrontal cortical areas. In turn, the PAG has strong access to the caudal medullary NRA. The NRA is the only cell group that has direct access to the motoneurons involved in vocalization, i.e., the motoneuronal cell groups innervating soft palate, pharynx, and larynx as well as the diaphragm, intercostal, abdominal, and pelvic floor muscles. Together they determine the intraabdominal, intrathoracic, and subglottic pressure, the control of which is necessary for generating vocalization. Only humans can speak, because, via the lateral component of the volitional or somatic motor system, they are able to modulate vocalization into words and sentences" (Holstege and Subramanian 2016).

Another brainstem area with relevant morphological data to be linked with functional and clinical implications is the substantia nigra (SN, van Domburg and ten Donkelaar 1991).[18] The human SN presents an interindividual variability in shape, asymmetry, and volume in normal individuals (50–91 years of age; Di Lorenzo Alho et al. 2016). Comparing the SN *pars compacta*, *pars reticulata, and pars diffusa*, the former contains large neuromelanin-rich neurons (Braak and Braak 1986; Di Lorenzo Alho et al. 2016). Cells usually superimpose each other in the heterogeneous SN parts, although showing distinct morphological, pigmentation, and histochemical features (Braak and Braak 1986; Halliday et al. 2012).

Three types of neurons were identified in the SN of individuals 20–93 years old: "Type I," mainly found in *pars compacta* (but also in *pars diffusa* and less in *pars reticulata*), is a medium-sized to a large cell with neuromelanin granules in the cell body. They are tyrosine hydroxylase-immunopositive projecting neurons with a triangular or polygonal cell body shape or, in a few cases, spindle, bitufted soma (Braak and Braak 1986; Halliday et al. 2012; Fig. 9.7a, b). Type I dopaminergic cells have two to six thick and sparsely branching dendrites, frequently as one large and other smaller primary dendrites with a straight extent and smooth aspect, or with some segments with small-sized spines (Halliday et al. 2012; Fig. 9.7a). Extended thick dendrites form small bundles into the *pars reticulata*, but not beyond nuclear boundaries. Neurons in *pars diffusa* may send dendrites into the perirubral formation. The heterogeneous distribution of dendritic spines is evident in these type I neurons. Spines can be sparse along dendritic shafts, forming isolated patches of grouped spines, or show a high density of pleomorphic spines, some as "thorny appendages" (Braak and Braak 1986, Fig. 9.7a, b).

"Type II" neurons, mainly found in the *pars reticulata* and *pars diffusa* (less in *pars compacta*), are usually non-pigmented and have a variable size (usually slightly smaller than type I cells). The cell body shape is determined by the number of primary dendrites. Slender and elongated cells with two dendrites at opposite cell body poles are most commonly observed followed by other multipolar forms with more

[18]The morphology, neurochemical profile, and number of affected SN *pars compacta* neurons relate the pathophysiology of Parkinson's disease (PD; Gibb and Lees 1991). Recently, single-nucleus RNA-sequencing profiling of human SN *pars compacta* dopaminergic neurons identified a population that is selectively vulnerable and degenerates in PD (Kamath et al. 2022). These neurons have a unique, very large, dense, and widely spread axonal arbor architecture targeting the neostriatum (Matsuda et al. 2009), which might impose a chronic high energetic demand and likely damaging oxidative stress (Bolam and Pissadaki 2012; see additional comments in Giguère et al. (2018) and recent findings in an animal model in Ferreira et al. (2020)). There are various intracellular molecular changes in human SN dopaminergic neurons critical to the neurodegeneration and symptomatic manifestations of PD (Halliday et al. 2005), but the loss of neurons in this disease is not confined to the SN. Morphological and functional impairments include motor and nonmotor circuits, and PD progression alters the olfactory bulb, other brainstem areas, temporal mesocortex, and neocortical areas (Braak et al. 2003; Bolam and Pissadaki 2012; Giguère et al. 2018). For example, the pedunculopontine nucleus in the ponto-mesencephalic tegmentum is part of the mesencephalic locomotor region and may be involved in sleep and cognitive disturbances (French and Muthusamy 2018) at different stages of PD progression (Braak et al. 2003; see also Rietdijk et al. 2017). Many patients also suffer from hallucinations and delusions.

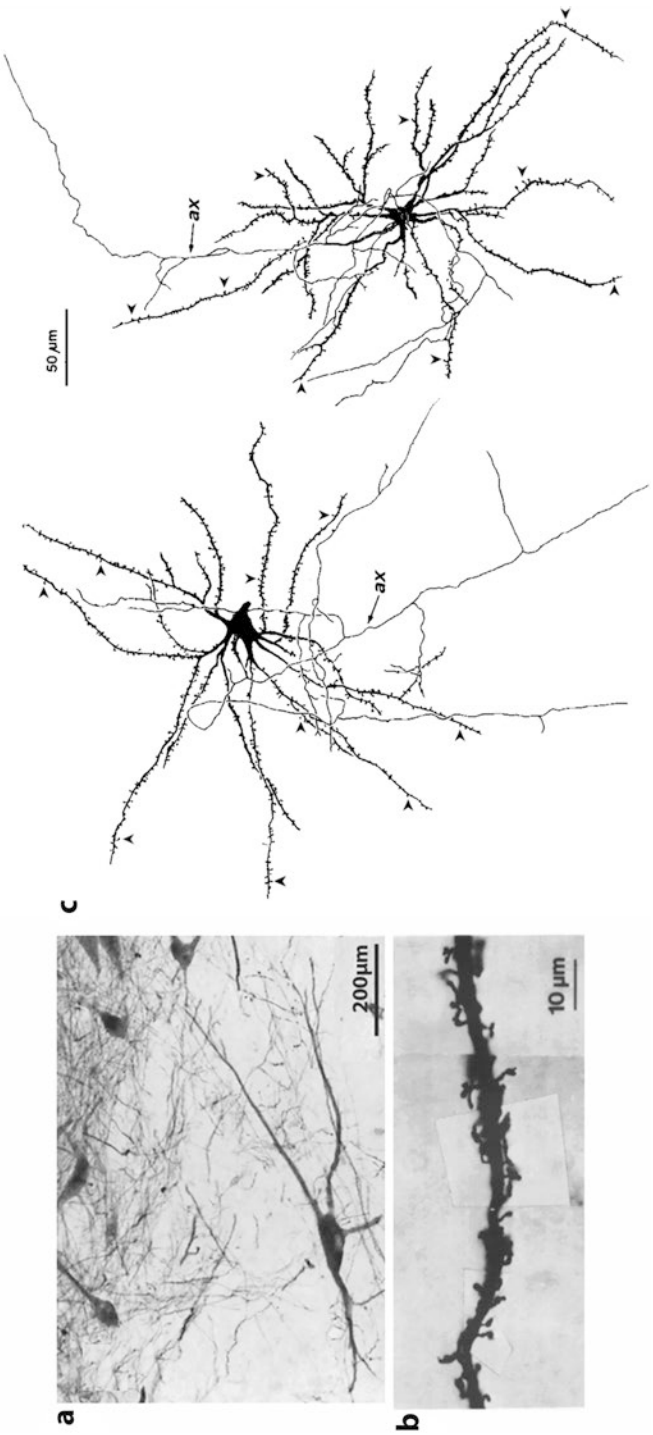

Fig. 9.7 (**a**) Typical medium-sized to large tyrosine hydroxylase-immunoreactive dopaminergic neuron found in the human substantia nigra *pars compacta*. These neurons characteristically contain neuromelanin pigment and are projection cells. [Image originally published in "The Human Nervous System," 3rd edition, by Halliday et al. "Substantia Nigra, Ventral Tegmental Area, and Retrorubral Fields," p. 439–455, reproduced under license #221112-000190, Copyright Elsevier (2012)]. (**b**) Golgi-impregnated dendritic segment from the same type of dopaminergic neuron as in (**a**), also classified as a "type I" cell. Although such neurons can show many smoothly contoured thick dendrites, some dendrites also display spines and "spine-like protrusions" as shown in this image. (Figure reproduced from Braak and Braak (1986), originally published and copyrighted by Springer Verlag). (**c**) Camera lucida drawing of Golgi-impregnated medium-sized spiny neurons of the human striatum. Note the highly ramified arbors with branches radiating in all directions. Spines (arrowheads) are found after the initial segments of the main dendritic shafts and along various collateral branches. Spines also occur in the axon hillock (*ax*, pointed by an arrow in the neuron at the center of the figure). (Legend and figure reprinted from Braak and Braak (1982b) under CCC RightsLink® license #5386640793281, originally published by Springer Verlag)

than two primary dendrites and some collateral branches near the cell body. Smooth primary dendrites give rise to intermediate and distal dendritic segments with a low density of isolated spines or clusters of spines. "Type III" neurons, in all SN portions, have usually a small cell body with varied shapes. A few thin primary dendrites radiate in various directions, which, as a rule, show very few branches and are spineless shafts. These cells show lipofuscin granules that did not tend to agglomerate (Braak and Braak 1986).

Two types of non-pigmented, non-dopaminergic SN neurons are immunoreactive to the calcium-binding proteins calretinin and parvalbumin. Calretinin-containing neurons have two primary dendrites emerging from opposite somatic poles and are observed surrounded by pigmented cell clusters only in *pars compacta*. Parvalbumin-containing neurons concentrate in *pars reticulata* and are small multipolar cells with round or triangular cell bodies and dendrites with few branching points (Halliday et al. 2012; see Damier et al. 1999 for calbindin immunohistochemistry distribution within the human SN).

The human dentate nucleus, one of the cerebellar central nuclei, consists of 6–10 irregular rows of closely packed cells that, compared to other mammals, have smaller neurons with thinner, shorter, and less branched cells (Cajal 1909–1911). Peters et al. (1991) depicted a Golgi-impregnated small neuron in the dentate nucleus of the cerebellum. This cell has an ovoid cell body and multiple primary dendrites. The thickest primary shafts radiate and immediately branch around the cell body. Thin primary branches are straight or tortuous and show few branching points. Dendrites of different branching orders are found close to the cell body with a radial orientation. There are few spines with a heterogeneous distribution. Some dendritic segments are smooth. Other dendritic segments have isolated spines, spines at a low density along the dendritic length, or pleomorphic spines in distal parts (Peters et al. 1991).

Purkinje cells in the human cerebellar cortex display thick and short proximal primary, secondary, and tertiary dendrites devoid of spines or showing isolated spines. Phylogenetic differences are found in climbing fibers and dendrites of Purkinje cells in humans. In these latter, after proximal ramifications, further branched dendrites have spines along their extensions, which are so close that they almost touch. These spines are abundant and of varied sizes, which include short and thick or long and thin spines, as depicted by Cajal (1909–1911).

In the human cerebellar cortex granular layer, three types of large nerve cells were identified in samples from 37- to 55-year-old individuals (Braak and Braak 1983a): (1) Most cells are "Type I" neurons, also found in the Purkinje cell layer, and correspond to the Golgi cells with a rounded or polygonal cell body. Only a few dendrites usually arise from various sites of the cell body, radiating in all directions with few branching points, and forming a globular dendritic domain. These dendrites show little reduction in diameter along their extension and collateral branches often do not taper significantly compared to the parent dendrite. Very few spines are found along the dendritic length of these Golgi cells. They are "small kinks and twists and even single spines." (2) "Type II" cells (found even within the white matter) show a fusiform, triangular, or polygonal cell body, generally with a few primary dendrites. These dendrites are remarkably long and straight, extending up to

700 μm away from the soma, and rarely branching or, distally, ramifying up to two times. Horizontal dendritic shafts are often densely covered with "stalked" (thin) spines. Finally, (3) "Type III" cells are heterogeneous large multipolar neurons with varied shapes, including spindle and triangular aspects, and broad distribution (also within the Purkinje cell layer and the white matter) but a small number. They display two to eight primary dendrites, which show different features. For example, some dendrites are long straight shafts that do not ramify or, when dividing, generate secondary branches distally. Other cells display a dense dendritic arborization close to the cell body whereas others have a straight dendrite that ramifies profusely distally. Intermediate morphological aspects for branching patterns are observed as well. Notably, some dendrites project toward and extend into the deep portions of the molecular layer and the Purkinje cell layer. Dendrites are smoothly contoured for the most part, although some "small appendages" and spines are occasionally observed (Braak and Braak 1983a). After this description, another type of monodendritic neuron was reported in the human cerebellar granule cell layer. It is a calretinin-immunoreactive bipolar cell with a characteristic spherical, ovoid, or more elongated cell body, a single very thick and short primary dendrite with no preferential orientation terminating in a closeby tuft of short and fine arborizations with small swellings or leaflets, and a thin axon emerging from the cell body (Braak and Braak 1993).

These data address the functional organization of the afferent, intrinsic, and efferent cerebellar circuitries in humans (see fundamental data in Voogd and Ruigrok 2012). It is noteworthy that the dendrites of Purkinje cells are spiny, but the presence and density of spines are variable in different granular layer neurons. Purkinje cells compute and rather modulate a huge amount of afferent synaptic inputs along the dendritic tree before determining their firing pattern as the cerebellar cortex efferent pathway. With the number of contacts ranging between 200,000 and 1 million per cell, the location and kind of synaptic inputs along the Purkinje cell dendritic tree are controlled, integrated with intrinsic membrane properties, and determine the cellular excitability and pattern of firing output (Llinás and Sugimori 1980; Bastian and Lisberger 2021). On the other hand, granular cells can integrate information along the extension of long dendrites, some without ramification, which suggests direct synapses on dendritic shafts and distinct cable properties based on such structural dendritic organization. In our species, the cerebellum reaches maturity after birth (as the neocortex), enabling further motor skills during childhood as well as continuing to show plastic properties for memory and learning of planned motor behavior and other nonmotor functions along our lifespan (Diamond 2000; Bastian and Lisberger 2021; Kolb and Whishaw 2021).

9.4.4 Thalamus and Basal Ganglia

Multiple spiny multipolar neurons are found in the thalamic "somatosensory nucleus" of cats, rabbits (Cajal 1909–1911), rats, and mice (Scheibel and Scheibel 1967). In humans, thalamic neurons in the superior region, including the anterior

nuclear group and the dorsal superficial nucleus, show round to polygonal cell bodies and are typically isodendritic, some with marked ramification close to the soma (Mai and Forutan 2012). There are principal/projection cells and interneurons in different thalamic nuclei (Braak and Weinel 1985). In the medial region, represented by the mediodorsal nucleus and subdivisions, there are characteristic very large, polygonal or flattened cells in the paralaminar (lateral) component; the paratenial nucleus of the periventricular formation contains medium-sized triangular neurons with thin and long processes; and neurons in the inferior pulvinar nucleus in the posterior thalamus show a predominance of smaller cells with a polygonal cell body and various thin proximal processes (Mai and Forutan 2012).

The nuclei composing the lateral region of the thalamus are functionally involved with processing and relaying relevant information for sensory and motor modulation in humans (Mai and Forutan 2012). As an initial hypothesis, it would be expected that neurons in this region would display a variety of spines for the synaptic computation of multiple inputs and for sending a modulated output firing pattern toward the next circuitry steps. Surprisingly, it is not the case for the dendrites in the adult human neocortex-dependent nuclei of the lateral thalamus. These neurons are devoid of spines or show very few long and thin protrusions ("appendages") or stalks without spine heads (Braak and Braak 1984a). In other words, (1) "Type I" neurons have a polygonal cell body and various radiating primary dendrites (three to seven), which branch profusely and generate a dense and mostly globular dendritic field. According to the territory where these cells are located, they can also display a bush-like dendritic arbor with branches mainly oriented in one preferred direction. Typical spines are absent on dendrites. Rather, thread-like appendages are present, which display elongated stalks lacking a terminal knob. (2) "Type 2" neurons show cell bodies smaller than type I cells, elongated, spindle-shaped, or polygonal with some primary dendrites (e.g., four to five), which ramify sparsely and proximally providing an ellipsoidal dendritic domain with few branches. These local circuit cells have smooth shafts or, along the extension of the dendritic tree, isolated or very few spines are observed in restricted dendritic segments. (3) "Type 3" neurons have polygonal medium- to large-sized cell bodies and thick, short primary dendrites that ramify close to the cell body. Dendrites have a straight or slightly curved course extending in all directions. These cells do not show spines or other appendages (Braak and Braak 1984a). In this same thalamic area, medium-sized multipolar neurons with a fair number of typical dendritic spines were observed forming small cellular islands near the boundaries of the intralaminar nuclei. These cells were named "ectopic neurons" by Braak and Braak (1984a).

Visual processing pathways activate and are modulated by the thalamus and metathalamus. Novelty seeking and interaction with the world by exploring visual objects involves the zona *incerta* in primates (Ogasawara et al. 2022), an extension of the reticular nucleus of the thalamus related to visceral functions, arousal, and attention (Zrinzo and Hyam 2018). In the visual metathalamic pathway relay station, the lateral geniculate nucleus process visual information modulated by selective attention. It integrates retinal and brainstem nuclei inputs with top-down signals from corticothalamic feedback projections (Reynolds et al. 2013). Neuronal types in the lateral geniculate nucleus show smooth dendrites or few spines in adult

humans. “Type 1” projecting cells (the most abundant) are heterogeneous medium- to large-sized polygonal and spindle-shaped cells with two to ten radiating primary dendrites of varied features. The variety of shapes for these multipolar neurons is notable. Some cells have two thick primary dendrites emerging from one pole of the cell body and the axon hillock at the other pole. Dendrites can have isolated or clustered “excrescences” (i.e., protrusions with a blunt aspect or with a long and thin gnarled outline, some of them resembling thin, wide, and large complex spines) placed close to proximal branching points. Few pleomorphic dendritic spines were found isolated along the extension of the dendritic tree and rarely exist along thin distal segments. Another type I neuron possesses thin, radiating, and smoothly contoured dendrites with few dendritic excrescences or thorny appendages. “Type 2” and “Type 3” cells (interneurons) usually have a small round, ovoid, triangular, or spindle-shaped cell body. They have two to four primary dendrites, some with a tufted aspect, others with sparse branching and straight, smooth dendrites forming an ellipsoidal domain. Dendritic spines are not found along the dendritic shafts and branches, except for the occurrence of rare irregularly distributed thorny appendages. In their distal portions, Types 2 and 3 neurons have dendrites whose appearance resembles thin axon-like structures (Braak and Braak 1984b; Braak and Bachmann 1985). These and other thalamic components, such as its centromedian nucleus, surely deserve more attention and in-depth histological and functional studies (Ilyas et al. 2019).

The basal ganglia is part of a circuit involving the cerebral cortex, hippocampus, amygdaloid complex, thalamus, and brainstem nuclei to elaborate, execute, and learn new planned, motivated behaviors requiring executive function, motor adjustments, cognitive, and emotional processing (Smith and Bolam 1990; Haber et al. 2012; Horak and Earhart 2021). The cytoarchitecture and multiple functional circuitries of the striatum have been investigated in humans and other species (Cajal 1909–1911; Smith and Bolam 1990; Haber et al. 2012; Lanciego et al. 2012). Input projections (sensorimotor, associative, and limbic), intrinsic connections, and outputs of the basal ganglia form a series of reentrant parallel projecting functional loops under within and outside modulatory actions (Redgrave and Costa 2021).

The neostriatum receives inputs from cortical and subcortical areas that innervate local medium spiny neurons, including dopaminergic neurons from the SN (Smith and Bolam 1990). There are important features involving the synaptic organization and functioning of this circuit. First, inputs from the cerebral cortex and the central lateral thalamic nucleus appear to make few individual contacts but extend their action upon many striatal neurons, whereas those from other areas (e.g., the parafascicular thalamic nucleus) might do the opposite for each cell make various contacts to influence few local neurons (Redgrave and Costa 2021). Second, the complex axonal arbor of each SN projecting cell innervates a significant volume of striosome and matrix compartments of the neostriatum (Matsuda et al. 2009). In rats, it is estimated that approximately 75,000 striatal neurons might be innervated by a single dopaminergic neuron, and one striatal neuron might be under the influence of 95–194 of these dopaminergic cells (Matsuda et al. 2009). In humans, it is estimated that one single dopaminergic neuron from the SN *pars compacta* gives rise to between 1 and 2.4 million synapses at the level of the striatum (Bolam and Pissadaki 2012). Third, there are

different patterns of synaptic innervation and organization on the spines and dendrites of striatal neurons (Smith et al. 1994, 2004). Striatal medium spiny projection neurons are targeted by corticostriatal, thalamostriatal, and dopaminergic input axons. Corticostriatal inputs converge on the head of dendritic spines, most nigrostriatal inputs converge on the neck of dendritic spines, and most thalamic terminals from caudal intralaminar nuclei form asymmetric synapses on dendritic shafts (in rats and monkeys; see complete data in Smith and Bolam (1990), Smith et al. (2004)). Furthermore, thalamostriatal afferent fibers generate strong synaptic inputs in proximal dendrites and perikarya of striatal cholinergic interneurons, while corticostriatal inputs are scarce on distal dendrites (Smith et al. (2004) and references therein). Thalamic and dopaminergic inputs usually are not nearby or have synaptic relationships when innervating the same postsynaptic target in the sensorimotor territory of the striatum in monkeys (Smith et al. 1994).

These data indicate morphologically tuned synaptic processing adjusted for each input source as well as the integration of varied information by medium spiny neurons before projecting an output code toward parallel striatal functional loops. The importance of these integrated actions is reflected in the fact that, besides the components of the classical "direct" and "indirect" circuits, other relevant output pathways connect the striatum with the superior colliculus, periaqueductal gray, pedunculopontine, parabrachial nuclei, and nucleus *accumbens* (Smith and Bolam 1990; Redgrave and Costa 2021). The involvement of various brain areas and circuits with the striatal medium-sized spiny neurons provides research avenues to investigate the diversity and magnitude of clinical manifestations, including emotional disturbances, in the course of neurodegenerative Parkinson´s and Huntington´s disease, for example.

Cajal (1909–1911) and Braak and Braak (1982b) detailed the morphology of neuronal types in the striatum of humans. Cajal described the morphology of three main neuronal types, namely, (1) particularly in the caudate nucleus, a more or less spherical to polygonal small to medium-sized neuron with a short axon or with an axon projecting throughout a broad region of adjacent striatal nucleus or nuclei. These cells have a large number of spiny, moderately branched, radiating, and rather short dendrites; (2) large cells (with fusiform, triangular, or polygonal soma and rare Nissl granules) and rare giant stellate cells (with Nissl bodies in their cytoplasm) with a characteristic long axon and long, stout, and moderately branched dendrites covered with many spines; and (3) "dwarf or neurogliaform neurons" with a small spherical soma, several short varicose dendrites, and short axon (Cajal (1995)—see Fig. 325 for his drawings of neuronal types from a human infant brain).

Braak and Braak (1982b) reported the following five types of Golgi-impregnated neurons in the striatum of adult individuals (44–52 years old): (1) "Type I," the most abundant cell, is the typical medium-sized neuron with spiny dendrites. Four to 10 primary spine-free dendrites emerge from a spindle-shaped or polygonal cell body. Close to the soma, dendrites ramify and various second-order branches follow a relatively straight course. Secondary and further orders branches show many thin spines with different sizes. Mushroom and stubby spines were also observed (Fig. 9.7c; see also Fig. 2 in Braak and Braak 1982b). Taking into account the local

connectional organization, "dendrites radiate in all directions, but in places, especially close to thicker bundles of myelinated fibers, they are more or less strictly oriented in parallel to the fascicles." Also noteworthy, the axons of these cells can show a few stubby "appendages" proximally, can ramify within the dendritic domain of the parent neuron, and then project forward (Fig. 9.7c). The identification of such Golgi-impregnated axons implies that projection fibers and local ramified collaterals lack a myelin sheath. (2) "Type II" is a medium- to large-sized cell with long intertwining dendrites covered with spines of uncommon shape as well as somatic spines. The cell body is triangular, spindle- or horn-shaped from where emerge a few very thick primary dendrites. These dendrites ramify repeatedly and show a gnarled varicose aspect. Thin terminal branches have a curved course and form a small dendritic domain. There is a moderate number of pleomorphic spines, including "stubby protuberances" and "a fair number of spicular appendages with elongate pedicles." Perikarya and proximal dendrites are covered with "knobbed spines" (see Figs. 3 and 4 in Braak and Braak 1982b). (3) "Type III" is a large spindle-shaped or multipolar neuron with thick extended dendrites, few branching points, and isolated spines along intermediate to distal dendrites. (4) "Type IV" is a large aspiny cell with a rounded cell body and richly branching tortuous thick and thin primary dendrites. These neurons have a dense radial dendritic domain made by many relatively short dendrites close to the cell body. Although considered "aspiny," slender terminal dendritic branches have a gnarled appearance and varicosities and a "few isolated peduncular spines." (5) "Type V" are small- to medium-sized round aspiny cells with only a few relatively thick dendrites that ramify close to the soma. Beaded branches and fine terminal collaterals form a small ellipsoidal dendritic domain. Although dendrites are rather smooth, a "few isolated and minute thorns" can also be observed along the dendritic arbor (Braak and Braak 1982b).

Braak and Braak (1982a) also described five types of neurons in the human claustrum. Among large and small aspiny or "almost aspiny" nerve cells, it is significant the predominant occurrence of local Golgi-impregnated "pyramidal-like" spiny neurons - with no spines at proximal dendritic shafts and an evident number of pleomorphic spines along intermediate dendritic segments - or "modified pyramidal cells" (see Figs. 1–3 in Braak and Braak 1982a). These spiny neurons (likely projecting ones) would integrate reciprocal circuits with various cerebral cortex areas as well as would modulate information from amygdaloid nuclei in claustrocortical pathways (Fernández-Miranda et al. 2008).

9.4.5 Amygdala

The amygdala (or amygdaloid complex) is not a structural or functional unit; rather, it is composed of heterogeneous nuclei and subnuclei with particular phylogenetic, cytoarchitecture, connectional, neurochemical, and functional features (Brodal 1981; de Olmos et al. 1985; Gloor 1997; Swanson and Petrovich 1998; Rasia-Filho et al. 2000; DiMarino et al. 2016; Petrulis 2020), including "extended" areas outside

previously assumed anatomical borders (de Olmos 2004; Heimer et al. 2008; Yilmazer-Hanke 2012). The amygdaloid complex nuclei have both cortical and subcortical origins (Medina and Abellán 2012; Akhmadeev and Kalimullina 2015; Olucha-Bordonau et al. 2015) with pallial (most nuclei and their subdivisions) and subpallial components forming parallel circuits. These latter relate to the medial amygdaloid nucleus (MeA) and the central nucleus in the "extended amygdala" (CeA; Martínez-García et al. 2007)

The specialization of neuronal subpopulations in the amygdaloid complex likely provided more possibilities for sensory stimuli processing, for triggering somatic responses from primary emotions, and for associating them with complex social cues together with the gradual expansion of cortical circuitries (Janak and Tye 2015; Diano et al. 2017; Kerestes et al. 2017; Rasia-Filho et al. 2021; Šimić et al. 2021; Underwood et al. 2021). In this regard, the development of different amygdaloid nuclei would have contributed to important species-specific social behaviors, for example: (1) to further perceive and elaborate visual and auditory cues; (2) to attribute meanings and emotional valence to these stimuli; (3) to modulate new memories and cognitive abilities; and (4) to expand the behavioral repertoire for complex social interactions between individuals, including judgments of facial expressions and emotional vocalization contributing to behavioral displays of parenting, empathy, happiness, fear, or disgust (Adolphs 2003; Heimer et al. 2008; Rutishauser et al. 2011, 2015; Diano et al. 2017; Grisendi et al. 2019). That might have provided human brain networks with a higher level of information processing from cellular to network levels and from subcortical to cortical areas, with new emergent functional properties and adaptive responses.

The MeA, one of the phylogenetically oldest parts of the amygdaloid complex (Johnston 1923), has a relatively small area in humans (de Olmos 2004; Schumann and Amaral 2005). It contains five types of multipolar spiny neurons (Dall'Oglio et al. 2013). Golgi-impregnated neuronal types were morphologically classified in humans as (1) fusiform neurons with usually two (at most three) primary dendrites arising from opposite cell body poles, very long and straight dendrites with few branching points (Fig. 9.8a) or more branched shafts with a tufted aspect (see Fig. 2E in Dall'Oglio et al. (2015)); (2) neurons with a pear-shaped cell body, two primary dendrites emerging approximately at a right angle, branching sparingly, and showing very long shafts (Fig. 9.8b); (3) angular neurons with three primary dendrites that, despite the triangular cell body shape, do not display the characteristics of cortical-like pyramidal neurons (e.g., there is no evidence of one main thick apical shaft and two thinner and more branched basal shafts; instead, there are two main thick and long shafts with collaterals or three primary dendrites with almost similar thickness and branching pattern); (4) stellate neurons with a round or ovoid cell body and various primary dendrites radiating in multiple directions; and (5) rectangular neurons with four or more primary dendrites. The density of dendritic spines is variable in these human MeA neurons (Dall'Oglio et al. 2013). Close to the MeA, the human CeA possesses various neuronal types as well. All of them are spiny cells (unpublished observation).

The axonal morphology in the human MeA neuropil indicates various possibilities for synaptic contacts with local dendrites and spines. For example, there are "en passage" varicose fibers (probably for an ample "alarming" response evoked by inputs) as well as fibers with simple collateral prolongments with a terminal aspect. Other axonal collaterals display complex shapes, multiple branching patterns, and a bulbous ending that was further ultrastructurally related to a glomerular synaptic structure and function (Fig. 9.8c; see data in Dall'Oglio et al. 2013, 2015). Axons were observed crossing perpendicularly a restricted segment of spiny dendrites (Fig. 9.8d) and eventually having a terminal bouton close to a spine (Fig. 9.8e). These synaptic features are relevant to the human MeA role in neural networks that elaborate emotions (Blood and Zatorre 2001; Liberzon et al. 2003; Gamer et al. 2010), responding to aversive olfactory stimulation (Zald and Pardo 1997), to gonadal hormone-mediated premenstrual increase in stress-induced negative affect (Ossewaarde et al. 2013), and for the perception and processing of both aversive stimulus evoked by fearful faces and the positive valence of happy faces (Gamer et al. 2010).

In addition, the amygdaloid complex is related to the emergence and morphological heterogeneity of pyramidal neurons found in an anatomical and functional integrated subcortical–allocortical–neocortical *continuum* in the human brain (Rasia-Filho et al. 2021). The search for the emergence of pyramidal neurons led to the interface between subcortical and cortical nuclei of the amygdaloid complex and cerebral cortex transitional areas (Gloor 1997; Heimer et al. 2008; Insausti et al. 2017; McDonald and Duque 2022). Transition areas and nuclei with cellular components suggestive of a primitive cortex are found in the amygdaloid complex of primates (Amaral et al. 1992). In rats, the pallial amygdala is considered an initial allocortical structure characterized by superficial layered cortical areas and deep non-layered parts (Olucha-Bordonau et al. 2015). Likewise, a cytoarchitectonic organization in distinct layers was proposed for the human cortical amygdaloid nucleus (CoA; reviewed in Vásquez et al. (2018)). The CoA composes the "superficial cortex-like amygdaloid region" and is associated with the olfactory tract pathways together with other adjacent areas (see a critical discussion in Yilmazer-Hanke 2012). In conjunction, it would form a cortical transition area having the piriform and entorhinal cortices in the rostral part and the caudal piriform cortex and lateral entorhinal cortex in the caudal part (Olucha-Bordonau et al. 2015).

By composing the superficial amygdaloid nuclei and at the beginning of the limbic lobe, the CoA participates in somatosensory processing, associative learning, and distinct aspects of emotional processes (Heimer et al. 2008; Goossens et al. 2009; Bach et al. 2011; Yilmazer-Hanke 2012; Bzdok et al. 2013). For example, the CoA is connected to the prosubiculum, the dysgranular temporo-polar and perirhinal cortices, the agranular insula, and the lateral orbitofrontal cortex (Gloor 1997). The CoA neurons would also integrate multiple stimuli, as evidenced by connectivity-based parcellation of the superficial amygdaloid group, to modulate olfactory and emotional information in the context of social interaction and for approach-avoidance behaviors (Bzdok et al. 2013).

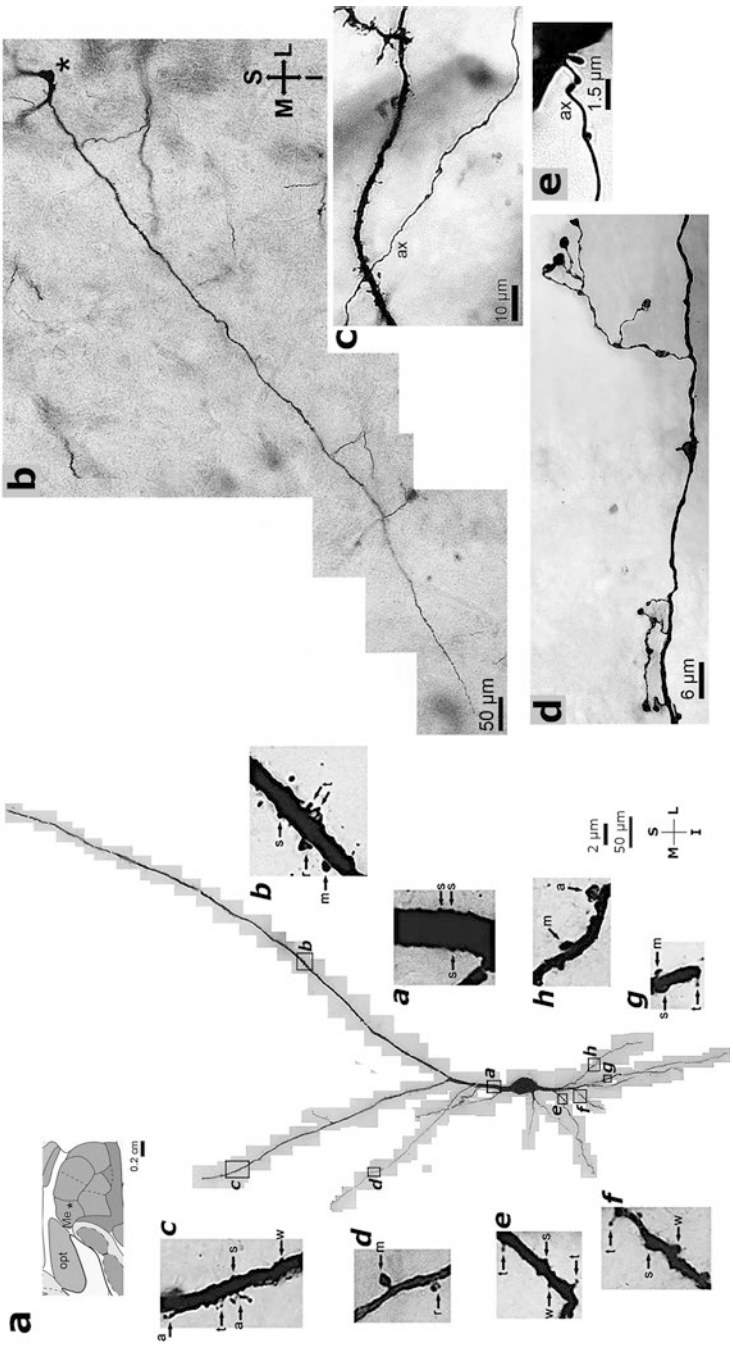

Fig. 9.8 *(caption on p. 423)*

Based on morphological criteria, ten Golgi-impregnated neuronal types were described in the human CoA, although three of them show some similarities to a pyramidal-like shape (Vásquez et al. 2018, 3D reconstructions available as Supplementary Images in Guerra et al. 2023). All are spiny neurons, but show differences in spine distribution and density along dendritic shafts (e.g., there is an impressive spine density in the unipolar neuron type shown in Fig. 15 from Vásquez et al. (2018)). Every type of spine is found in human CoA neurons. The 3D reconstruction of dendritic spines evidenced various shapes and sizes of stubby/wide, thin, mushroom, ramified, and transitional or atypical/polymorphic spines (Fig. 9.9a–e). The heterogeneous distribution, number, shape, and grouping aspect of spines along dendrites in the same neuron are exemplified by the pear-shaped cell in this brain nucleus (Fig. 9.9a–e; Vásquez et al. 2018). Note the "coralline excrescence" aspect of the highly packed dendritic spines with "numerous thin protrusions, velamentous expansions, and tendrils" (Fig. 9.9e, e'; classified according to Fiala and Harris 1999) and spinule protruding from different spines (e.g., Fig. 9.9c, d'; for structure, regulatory mechanisms, functions, and role of spinules in synaptic plasticity see Spacek and Harris 2004; Petralia et al. 2018; Zaccard et al. 2020).

Main dendritic shafts and collaterals in CoA neurons have longitudinal, transverse, and oblique orientations with a rather "planar" aspect within the neuropil volume. The number of neuronal types and their morphology suggest that cellular subpopulations developed to process differently the information from extrinsic and intrinsic circuits. In addition, the packing density and the existence of intermingled different neurons would allow afferent axons to contact more than one CoA neuron type to process the salience of the incoming stimulus. The diversity of spines also suggests that local cells might have different plastic possibilities for synaptic

Fig. 9.8 (**a**) Top: schematic diagram of a coronal section of the adult human brain showing the medial amygdaloid nucleus (Me) close to the optic tract (opt) 12 mm posterior to the midpoint of the anterior commissure. (Adapted from Mai et al. 2008). The asterisk indicates the location of a Golgi-impregnated large multipolar fusiform neuron shown as a composition of multiple digitized microscopic images obtained under light microscopy. Note the long dendrites and branching pattern, as well as the presence, distribution, density, and shape of dendritic spines. Spines are shown from samples (boxes *a* to *h*) along the dendritic length and corresponding inserts at higher magnification. Spines were classified as stubby (s), wide (w), thin (t), mushroom (m), ramified (r), or transitional/atypical (a, such as a double-spine in *c* and a spine with a racemose appearance in *h*). Photoshop CS3 adjustments (Adobe Systems, USA). I inferior, L lateral, M medial, S superior. Bars = 50 μm for the general view of the neuron and 2 μm for the inserts. (Legend adapted and figure reprinted from Dall'Oglio et al. (2015) under CCC RightsLink® license #5433161449807, originally published by John Wiley & Sons, Inc). (**b**) Reconstructed digitized microscopic image of another human medial amygdaloid Golgi-impregnated multipolar spiny neuron with a rounded, pear-shaped cell body, two thick primary dendrites, and few but long dendritic branches. (**c**) Straight axons cross perpendicularly dendrites in the Me neuropil, (**d**) show varicosities and collateral fibers with convoluted branching patterns and large bulbous endings, or (**e**) a small terminal bouton close to a spine head. (Legend adapted and figure reprinted from Dall'Oglio et al. (2013) under CCC RightsLink® license #5433161269561, originally published by John Wiley & Sons, Inc)

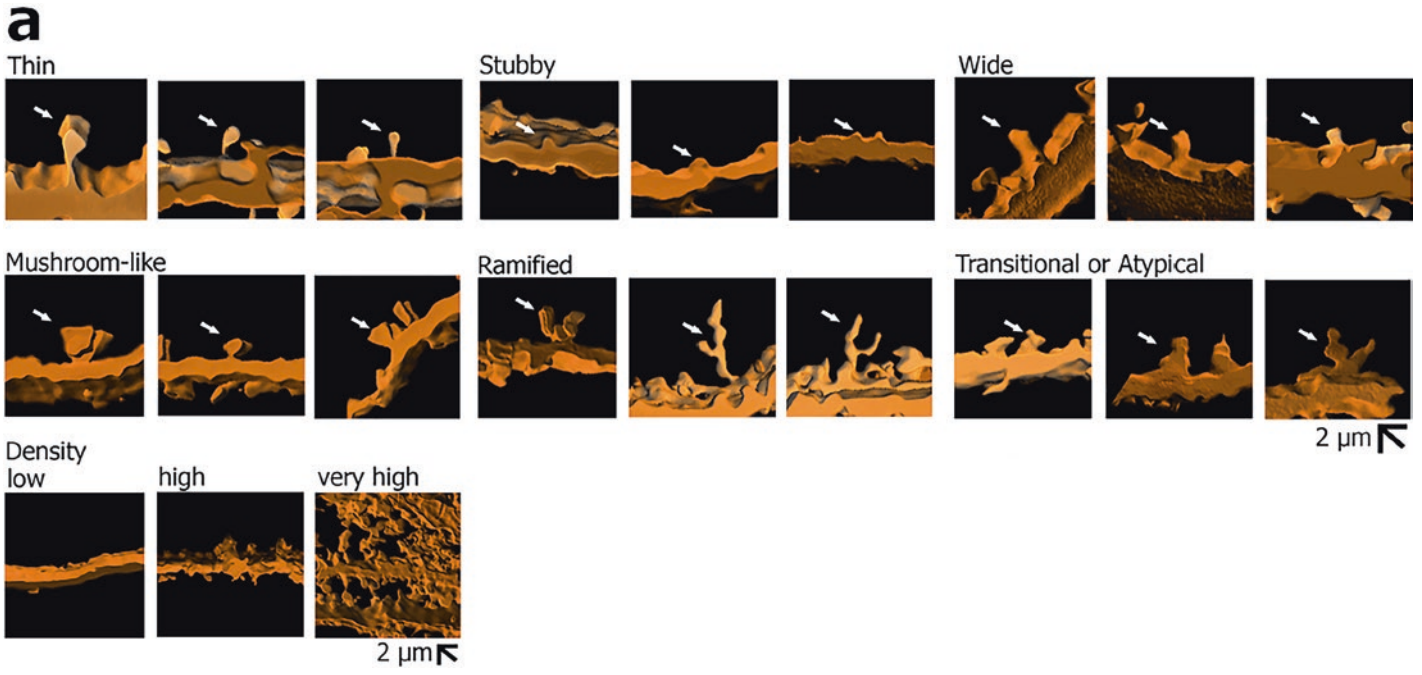

Fig. 9.9 (**a**) Three-dimensional (3D) reconstruction of Golgi-impregnated dendritic spines from the human cortical amygdaloid nucleus. Brightfield microscopy images were submitted to a segmentation model for the 3D reconstruction of spines. (Algorithm described in Reberger et al. (2018)). Spines were classified into different types, and the number of pleomorphic spines varies between dendritic segments, ranging from a low number of isolated spines to a very high density of clustered spines. (**b**) Golgi-impregnated pear-shaped neuron from the human posterior part of the cortical amygdaloid nucleus (PCO), 9.3 mm posterior to the midpoint of the anterior commissure. (Top, schematic diagram adapted from Mai et al. 2008). opt: optic tract. (Center) Reconstructed two-dimensional microscopic image showing the cell body and branched spiny dendrites. Examples of 3D reconstructed dendritic spines are shown in the inserts at higher magnification and different rotation angles (boxes *a-e* and corresponding inserts). Rotated segments are indicated by an apostrophe (*c'*, *c''*, *d'*, and *e'*).

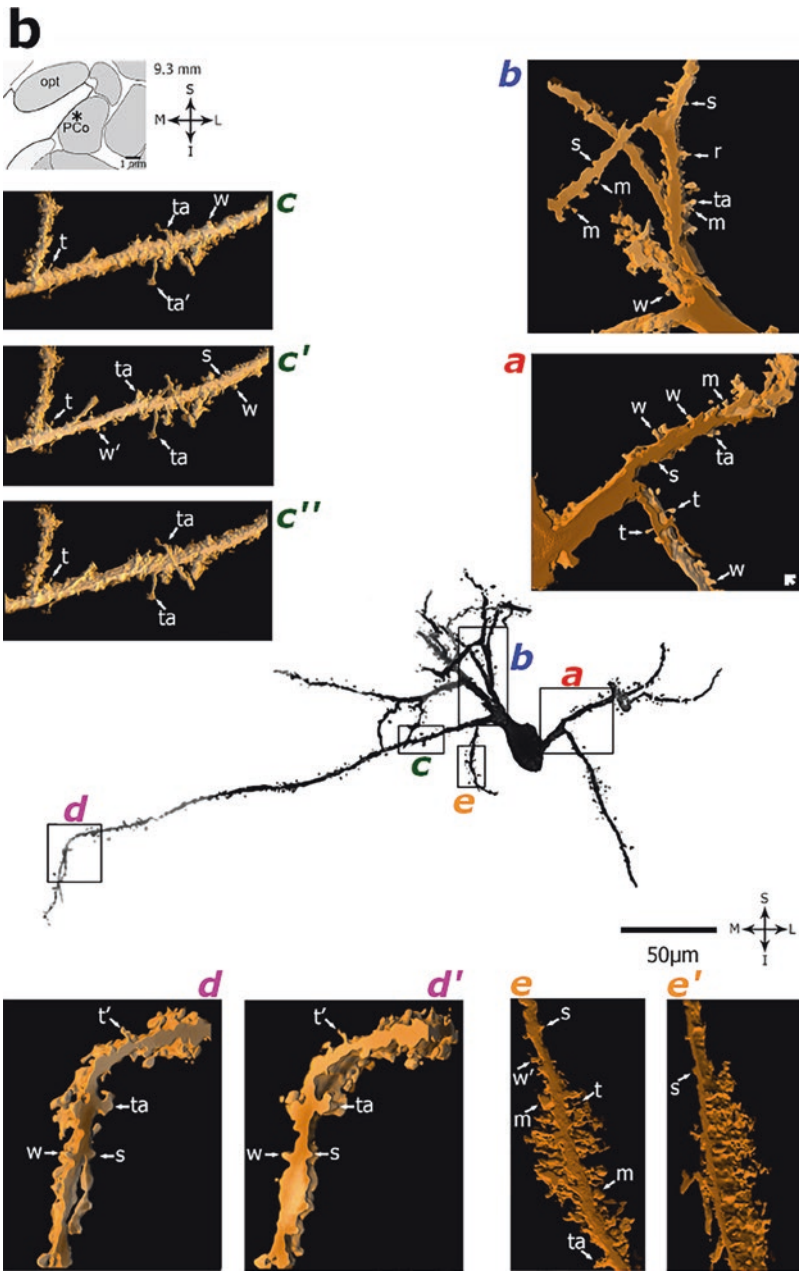

Fig. 9.9 (continued) The dendritic spine density varied from low (*a*) and moderate (*b* and *c*) to very high (*e*). Spines (arrows) were classified as stubby (s), wide (w), thin (t), mushroom-like (m), ramified (r), or transitional/atypical ones (ta). The presence of a spinule is indicated by an apostrophe in the corresponding spine (e.g., ta' in *c*, t' in *d* and *d′*, and w' in *e*). All images are from adult individuals. I inferior; L lateral; M medial; S superior. Scale bar = 50 µm for the neuron shape and 2 µm for the higher-magnification inserts (shown in (**a**)). (Legend adapted and figure reprinted from Vásquez et al. (2018) under CCC RightsLink® license #5384490072219, originally published by John Wiley & Sons, Inc)

modulation and computational possibilities, translating differently these input demands (Guerra et al. 2023). It remains to be determined how the CoA and adjacent areas participate in these circuits, from olfactory and emotional processing to cortical default mode network and cortical "dorsal attention subdivision" functions (Caparelli et al. 2017; Sylvester et al. 2020).

As mentioned above, the occurrence of spiny pyramidal neurons has an evolutionary and ontogenetic value *per se* in terms of increased connectivity and integrated functions in neural circuits (Spruston 2008; DeFelipe 2011; Marín-Padilla 2014; Sedmak et al. 2018; Petanjek et al. 2019; Rasia-Filho et al. 2021). The human CoA contains "pyramidal-like" neurons (Vásquez et al. 2018; Guerra et al. 2023; Fig. 9.10). These cells present a triangular cell body, one main thick apical dendrite, and two basal dendrites of a similar thickness at their emerging points. The apical dendrite ramifies close to the cell body and the main apical shaft is directed to the CoA surface. Both apical and basal dendrites have variable branching points and lengths. Some dendrites extend considerable distances away from the soma. Proximal dendritic shafts usually are smooth or show a few isolated spines. The density of spines increases along the dendritic segments (Fig. 9.10a, b). Pleomorphic spines include complex, atypical/polymorphic shapes, and spines with spinule (Fig. 9.10c, d, spines are shown at different rotation angles after using a supervised machine learning-based algorithm for 3D reconstructions of Golgi-impregnated human neurons).

It is noteworthy that the CoA and the components of the amygdaloid basolateral nuclei form the largest nuclear group within the amygdaloid complex. They progressed most in size along with the evolution that led to primates, displaying a coordinated development with the neocortex, and possessing more than 50% of all neurons in the human amygdaloid complex (Stephan et al. 1987; Gloor 1997; Schumann and Amaral 2005; Chareyron et al. 2011; Yilmazer-Hanke 2012).[19] Compared to rats, the large volume of the monkey amygdala relates to a greater expansion of the basolateral complex neuropil with a higher number of glial cells and more extensive dendritic and axonal arborization (Chareyron et al. 2011; Morgan and Amaral 2014). The lateral, basal, and basomedial (BM) nuclei are the primary targets of cortical and subcortical afferent projections to the amygdaloid complex in primates (Kelly and Stefanacci 2009). Inputs to the lateral amygdala come from the hippocampal formation, thalamic, and neocortical modality-specific

[19] The functional participation in cortical circuits is not restricted to a few amygdaloid nuclei. Due to multimodal input convergence from multiple parallel circuits, directly or indirectly, amygdaloid nuclei of different origins and in "a degree of mosaic evolution" and function can connect higher-order cortical areas (Hirata et al. 2009; Yilmazer-Hanke 2012; Kedo et al. 2018). For example, "being part of an organized neural network that projects to the bed nucleus of the stria terminalis and to various hypothalamic and brainstem nuclei, the CeA and MeA subnuclei also participate in social and defensive reactions against innate and learned threats with neuroendocrine, behavioral, and sympathetic/parasympathetic responses to fearful/defensive and stressful stimuli... The MeA projects to the periallocortical, paleocortex, and archicortex, as well as to the insular agranular cortex and ventromedial prefrontal cortex... These data indicate that the MeA also participates, although with varied magnitude, in parallel circuits with different parts of the evolved neocortex for social and emotional processing in our species" (Rasia-Filho et al. 2021 and references therein)

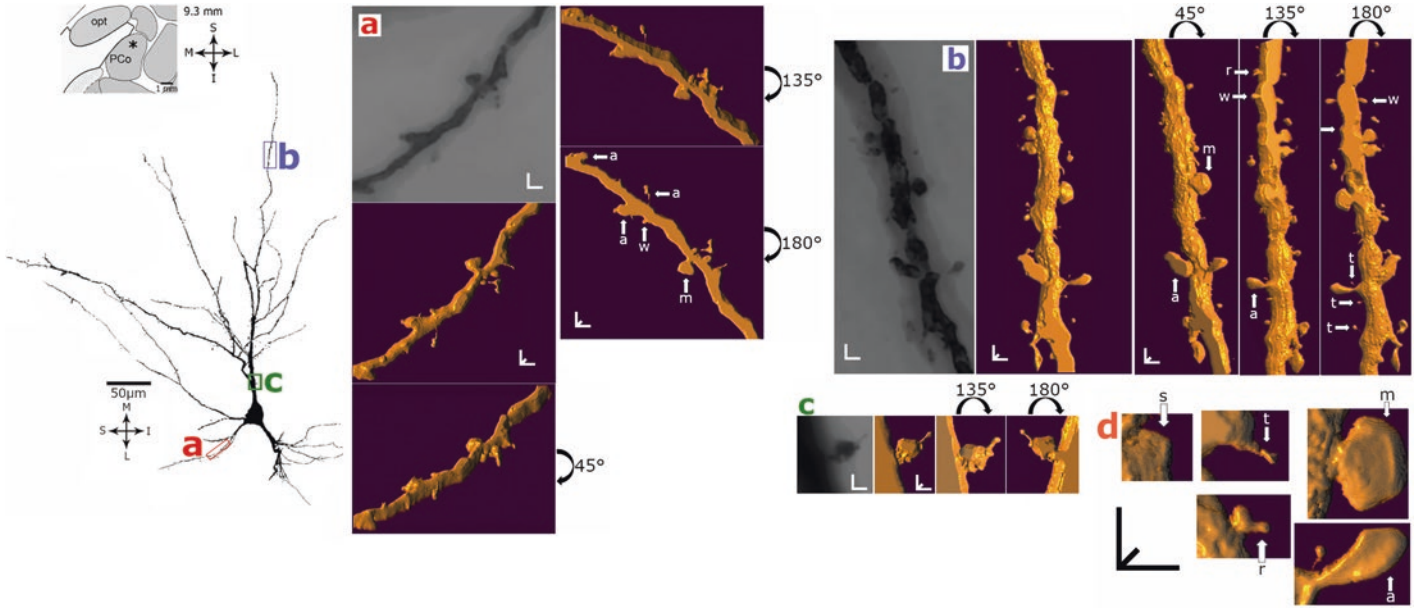

Fig. 9.10 Three-dimensional (3D) reconstruction of Golgi-impregnated dendritic spines from the human cortical amygdaloid nucleus. Brightfield microscopy images were submitted to a supervised machine learning-based approach for the 3D reconstruction of spines. (Described in Guerra et al. (2023)). (Left top) Schematic diagram of a coronal section of the human brain showing the posterior part of the cortical amygdaloid nucleus (PCO), 9.3 mm posterior to the midpoint of the anterior commissure. (Adapted from Mai et al. (2008)). opt: optic tract. (Left center) Two-dimensional reconstructed image illustrating the neuronal morphology under light microscopy. Boxes (**a**–**c**) indicate sampled segments in which 3D reconstruction of spiny proximal basal (**a**) and distal apical (**b**) dendrites showed varied spines number and shapes along the dendritic length. Curved arrows indicate that the 3D reconstructed images were rotated and are shown at different observation angles (**a**–**c**). In the inserts, dendritic spines (arrows) were classified as stubby (s), wide (w), thin (t), mushroom-like (m), ramified (r), or "atypical"/transitional ones (a), including a protruding spinule (**c**). Some examples of dendritic spines shapes and sizes are provided after 3D reconstruction at higher magnification in (**d**). Images are from an adult individual. Scale bar = 50 μm for the neuron shape and 1 μm for the dendritic spines in (**a**–**d**). I inferior, L lateral, M medial, S superior. (Legend adapted and figure reprinted from Guerra et al. (2023) under license #5441540588231 from CCC RightsLink® originally published by John Wiley & Sons, Inc.)

sensory processing areas to display responses to signal danger as quickly as possible and to initiate defensive behaviors without necessarily requiring additional neocortical processing (Janak and Tye 2015). In addition, the attention associated with the response to stimulus novelty and the amygdalo-hippocampal communication during the encoding of emotional stimuli can be translated into memory engrams and cognition (Rutishauser et al. 2015). The complexity of processing involving the human basolateral amygdala is further exemplified by its implication in late-life depressive symptom severity, associated with the dentate gyrus/hippocampal CA3 field and the lateral entorhinal cortex, during emotional episodic memory (Leal et al. 2017) and in the emotional content of dreams (Blake et al. 2019).

The human BM contains pyramidal-like (Fig. 9.11) and pyramidal (Fig. 9.12) neurons (Rasia-Filho et al. 2021, 3D reconstructions of these BM neurons available as Supplementary Figures in this reference). Pyramidal-like neurons show the apical dendrite ramifying close to the cell body while pyramidal neurons have a long apical shaft with a distal main ramification, and both may display different spatial orientations in the neuropil. These cells have branched basal dendrites and varied pleomorphic spines along the dendritic main shafts and collaterals (Figs. 9.10 and 9.11). Pyramidal-like neurons (or "modified pyramidal neurons") were also found in the human basolateral amygdaloid nucleus. They also show no preferential dendritic orientation within the neuropil and have apical and basal dendrites displaying several pleomorphic spines in secondary and further branched dendrites (see Fig. 5 in Braak and Braak 1983b). As observed from Golgi-impregnated samples, the spiny neurons of the accessory basal, basal, and lateral nucleus show different sizes, larger in the dorsolateral portions and gradually smaller in the ventromedial direction (Braak and Braak 1983b). Pyramidal neurons were also found in the lateral nucleus of the amygdaloid complex in humans (Sorvari et al. 1996).

The occurrence of morphologically and functionally specialized spiny pyramidal neurons and their organization in cortical areas might have represented a crucial form to develop circuits with proper wiring length and space (based on Guy and Staiger 2017; see also Cajal 1894; Chklovskii et al. 2002; Buckmaster 2017; Mercer and Thomson 2017; Narayanan et al. 2017). The morphological complexity of human pyramidal neurons varies along their emergence in areas initially considered as subcortical ones (e.g., some specific amygdaloid nuclei and the claustrum)[20] or transitional areas toward the allocortical, hippocampal regions, and the neocortical layers II-VI, with small pyramidal neurons in the upper layers II/III and large pyramidal neurons in the deep layer V (Ramaswamy and Markram 2015; Soltesz and Losonczy 2018; Cembrowski and Spruston 2019; Rasia-Filho et al. 2021), as shown in the following section.

[20] For the description of putative pyramidal neurons in the human basal nucleus of Meynert; see Mesulam et al. (1983), Saper and Chelimsky (1984), Morrison et al. (1987), and Liu et al. (2015). In rats, see the description of pyramidal-like neurons and Fig. 1F in Nakajima et al. (1985).

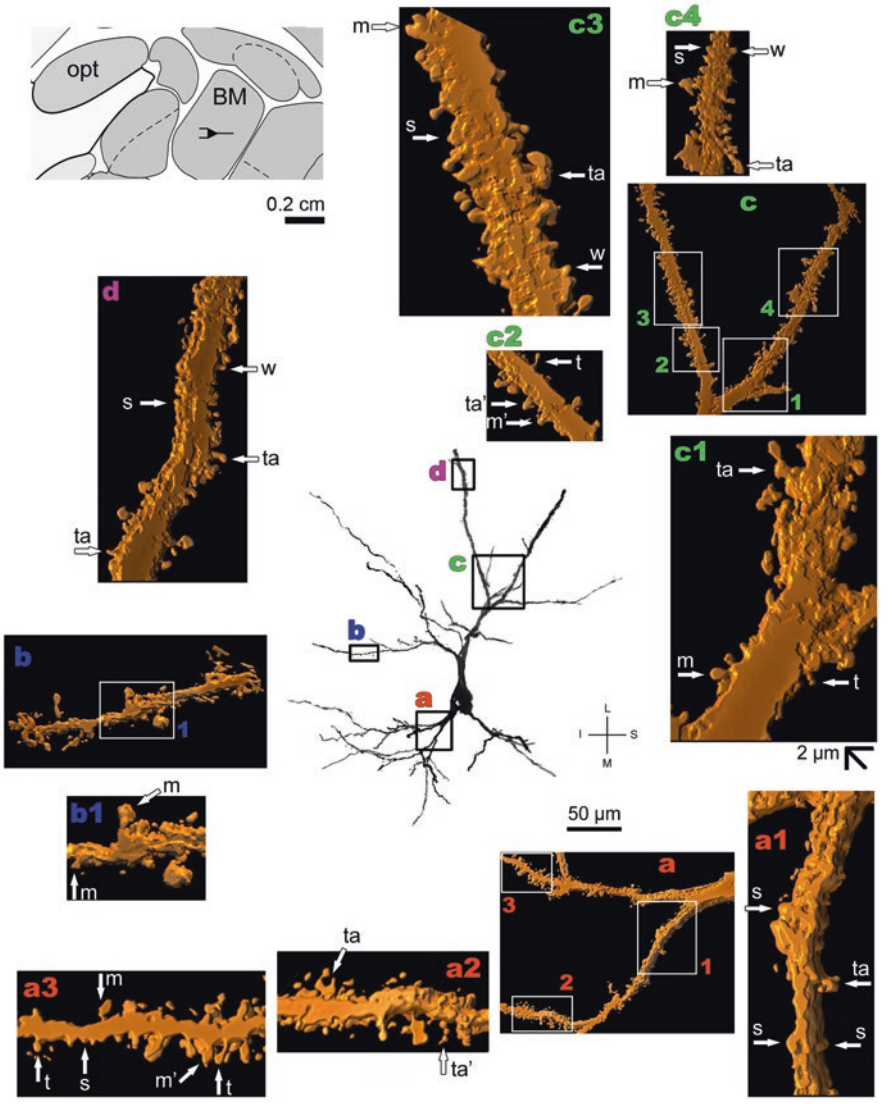

Fig. 9.11 Golgi-impregnated pyramidal-like neuron from the human basomedial amygdaloid nucleus (BM). (Top) Schematic diagram of a coronal section showing the human BM, 9.3 mm posterior to the midpoint of the anterior commissure. (Adapted from Mai et al. (2008)). opt, optic tract. (Center) Two-dimensional reconstructed image illustrating the neuronal morphology under light microscopy. The distribution, density, and shape of three-dimensional-reconstructed dendritic spines are shown in the inserts at higher magnification (**a**–**d**). Letters and numbers represent sampled parts of the same dendritic segment (**a1**–**a3**, **b1**, **c1**–**c4**). Note the high density of spines in the proximal basal dendrite (**a2**, **a3**) and along the intermediate to distal apical dendrites (**c1**, **c3**, **c4**, **d**). Spines were classified as stubby (s), wide (w), thin (t), mushroom-like (m), or transitional/atypical ones (ta). The presence of a spinule is indicated by the apostrophe attached to the corresponding spine (ta' in **a2** and **c2**, and m' in **a3** and **c2**). I inferior, L lateral, M medial, S superior. Images are from an adult individual. Scale bars = 50 µm for the neuron shape and 2 µm for the higher-magnification inserts (shown in **c1**). (Legend adapted and figure reprinted from Rasia-Filho et al. (2021) under CC BY license and Copyright © 2021 Rasia-Filho, Guerra, Vásquez, Dall'Oglio, Reberger, Jung and Calcagnotto)

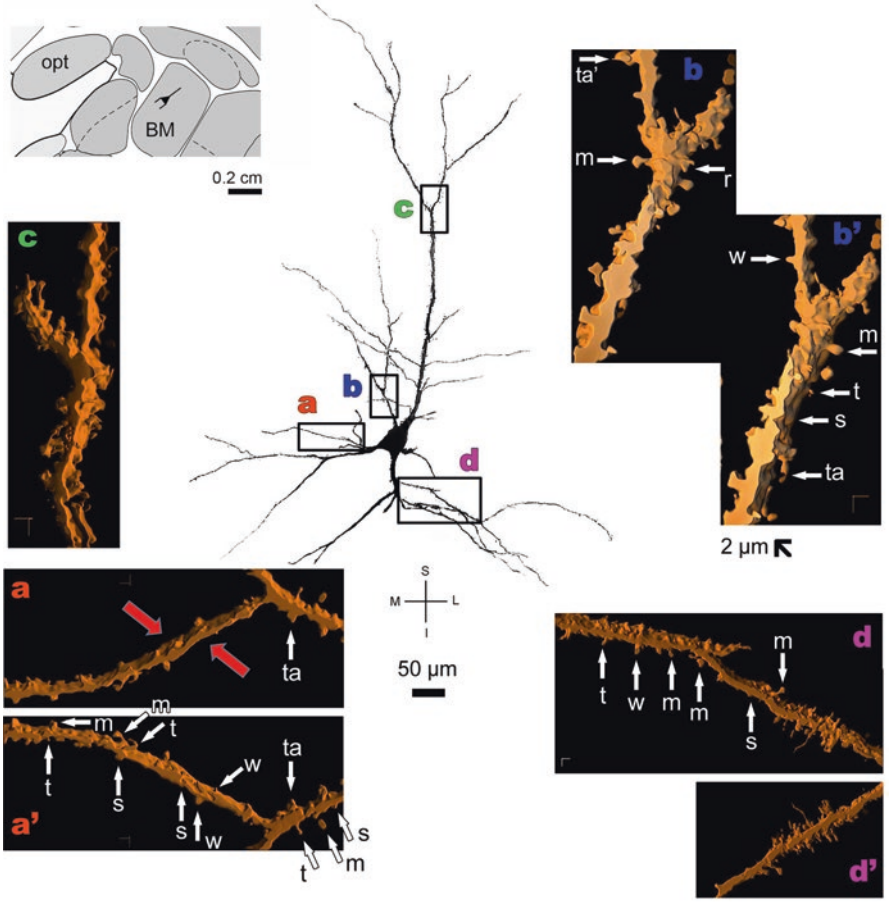

Fig. 9.12 Golgi-impregnated pyramidal neuron from the human basomedial amygdaloid nucleus (BM). (top) Schematic diagram of a coronal section showing the human BM, 9.3 mm posterior to the midpoint of the anterior commissure. (Adapted from Mai et al. (2008)). opt, optic tract. (Center) Two-dimensional reconstructed image illustrating the neuronal morphology under light microscopy. The distribution, density, and shape of three-dimensional-reconstructed dendritic spines are demonstrated in the inserts at higher magnification (**a**–**d**). The apostrophe over these letters represents an image that was rotated in space after reconstruction to show various pleomorphic dendritic spines (**a'**, **b'**, **d'**). Note that the same dendritic segment can have one side covered by spines and another side smooth (red arrows in **a**) There is a moderate (**a**, **a'**) to high (**d**, **d'**) density of spines in basal dendrites, proximal collaterals (**b**, **b'**), and distal apical dendrites (**c**). Spines were classified as stubby (s), wide (w), thin (t), mushroom-like (m), ramified (r), or transitional/atypical ones (ta). The presence of a spinule is indicated by the apostrophe attached to the corresponding spine (ta' in **b**). Images are from an adult individual. I inferior, L lateral, M medial, S superior. Scale bars = 50 µm for the neuron shape and 2 µm for the higher-magnification inserts (shown in **b'**). (Legend adapted and figure reprinted from Rasia-Filho et al. (2021) under CC BY license and Copyright © 2021 Rasia-Filho, Guerra, Vásquez, Dall'Oglio, Reberger, Jung, and Calcagnotto)

9.4.6 *Hippocampus and Neocortex*

An evident finding in the cerebral cortex is the abundance and functional specialization of pyramidal neurons (70–85% of all cells in the gray matter; Nieuwenhuys 1994; DeFelipe 2011; Mohan et al. 2015; Eyal et al. 2016; Kolb and Whishaw 2021). Pyramidal-like or other variations of "classic" pyramidal cells might have increased the synaptic processing and computational properties of evolved neural networks across various species (Spruston 2008; Rasia-Filho et al. 2021). For human evolution, pyramidal neurons' structure, functional properties, and increased connections may represent a fundamental advance for the elaboration of our higher nervous capacities (referred to as "the psychic cells" by Cajal 1894). Much about hippocampal neurons and neocortical pyramidal neurons was discussed in previous sections of this chapter. Further data on hippocampal formation's cellular components, connections, electrophysiology, and relevant functions can be found in other relevant works (e.g., Andersen et al. 2007; Insausti and Amaral 2012; Kandel and LeDoux 2021). Here, some representative 3D reconstructed images illustrate such neurons and the diversity of dendritic spines in human cells.

Gloor (1997) included the prepiriform–periamygdaloid area as part of the evolving mammalian allocortex, homologous with the ventral portion of the lateral pallium of amphibians and reptiles. Following the allocortical and neocortical *continuum* for the occurrence and development of pyramidal cells, the human periallocortex (i.e., the presubiculum, parasubiculum, and entorhinal cortex) contain pyramidal neurons (Insausti et al. 2017). Likewise, pyramidal cells are key elements for the hippocampal formation functional organization and display different morphological features locally (Andersen et al. 2007; Soltesz and Losonczy 2018; Rasia-Filho et al. 2021). The intrinsic circuit for information flow involves a serial pathway with several collateral and feedback projections connecting the entorhinal cortex, dentate gyrus, CA3 and CA1 fields, and subiculum (Wyss and van Groen 1995). The human CA3 hippocampal region contains pyramidal-like neurons or "short cortical pyramidal neurons" with a shape and dendritic field adapted to the position of these cells in a relatively small tissue volume (Fig. 9.13). These cells show a short apical dendrite ramifying proximally and oriented to the medial surface of the brain. Two main thick basal dendrites generate various branches close to the cell body. Several small spines are found in proximal basal shafts, whereas other pleomorphic spines are found along with the extension of both basal and apical branches. These CA3 neurons display thorny excrescences (Fig. 9.13a–c, but also found in the human MeA as reported by Dall'Oglio et al. 2015), a complex spine type with multiple PSDs and synaptic microdomains (3D reconstructed in Stewart et al. 2014; Reberger et al. 2018).[21]

[21] The CA3 pyramidal neurons are critical for encoding, storage, and recall of associative memory along the mouse transverse (or proximodistal) CA3 axis (Sun et al. 2017), showing distinct projections to CA1 cells for processing nonspatial information in rats (Nakamura et al. 2013). Mice CA3 pyramidal neurons show heterogeneous morphology, afferent connectivity, and electrophysiology. Regular-spiking pyramidal neurons have complex spines (thorny excrescences) that receive monosynaptic mossy-fiber input and were found at any position along the radial axis of the CA3 *stratum pyramidale*. On the other hand, intrinsically bursting pyramidal neurons lack thorny excrescences ("athorny" cells), receive no or very few mossy-fibers input, and preferentially occupy distal CA3 parts closer to *stratum oriens* (Hunt et al. 2018).

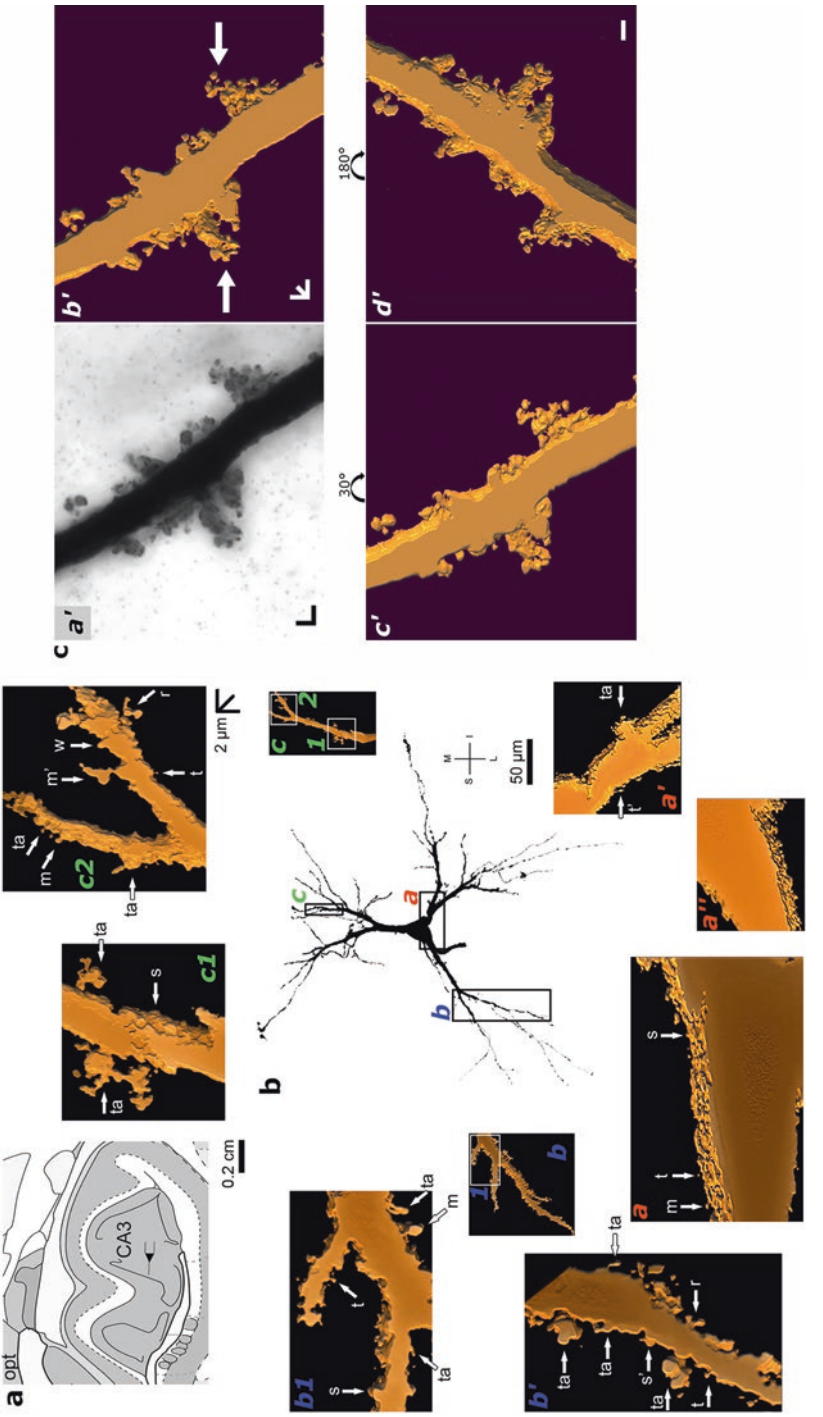

Fig. 9.13 (*caption on p. 433*)

The human CA1 hippocampal field shows a variety of pyramidal neuron shapes with different dendroarchitectonics and a variety of spine shapes and sizes, as revealed by the 3D reconstruction of Golgi-impregnated neurons under brightfield microscopy (Figs. 9.14 and 9.15; see relevant data based on fluorescent images for the dendroarchitecture of hippocampal cells in Benavides-Piccione et al. (2020)). Some CA1 neurons display basal and apical dendrites with a relatively short aspect and various branching points (Fig. 9.14), while other cells in deeper positions have straight and very long (at the order of millimeters) apical dendrites with scarce ramification (Fig. 9.15). Basal dendrites emerge at different points along the triangular or ovoid cell body. In both short and long CA1 pyramidal neurons, the apical dendrite is oriented to the surface of this brain area. These pyramidal cells coexist within the same neuropil volume and receive inputs at different dendritic fields (Benavides-Piccione et al. 2020). Basal and apical dendrites display an impressive number of pleomorphic spines, some with spinule (Figs. 9.14a–f and 9.15a–f). The basal dendrites of a long pyramidal neuron can show a huge density of pleomorphic spines along proximal to distal segments (Fig. 9.15a). Likewise, very long apical branches are covered by a huge density of all types of spines densely intermingled in the same dendritic segment (Fig. 9.15b–f, 3D reconstructions of human CA3 and CA1 hippocampal neurons available as Supplementary Figures in Rasia-Filho et al. 2021).

Morphological data suggest that hippocampal pyramidal neurons have a multitude of modulatory possibilities for the integration of information. Indeed, after noting the density of spines per cell, one has also to consider that there are approximately 16 million and 2.7 million neurons in human CA2-3 and CA1 hippocampal areas, respectively (West and Gundersen 1990). Synaptic inputs occur more on pleomorphic spines than on spine-free dendritic shafts in very long dendrites, which opens many possibilities to elaborate hypotheses on the morphological and functional relationships. For example, (1) how different spiny dendritic domains and

Fig. 9.13 Golgi-impregnated short pyramidal neuron from the human CA3 hippocampal region. (**a**) Schematic diagram of a coronal section showing the human CA3 region, 16 mm posterior to the midpoint of the anterior commissure. (Adapted from Mai et al. 2008). opt, optic tract. (**b**) Two-dimensional recon structed image illustrating the neuronal morphology under light microscopy. The distribution, density, and shape of three-dimensional-reconstructed dendritic spines are demonstrated in the inserts at higher magnification (*a-c*). Letters and numbers represent sampled parts of the same dendritic segment (*b1*, *c1*, *c2*). The apostrophe over the letters represents an image that was rotated in space after reconstruction to show various pleomorphic dendritic spines (*a'*, *a"*, *b'*). There is a high density of small spines in the proximal basal dendrite (*a*) and a moderate to high density of pleomorphic spines in intermediate dendritic segments of basal (*b*, *b1*, *b'*) and apical dendrites (*c1*, *c2*). Spines were classified as stubby (s), wide (w), thin (t), mushroom-like (m), ramified (r), or transitional/atypical ones (ta). Note the presence and shape of thorny excrescences in both basal (ta in *a'*) and apical (ta in *c1*) dendrites. The presence of a spinule is indicated by the apostrophe attached to the corresponding spine (t' in *a'*, s' in *b'*, and m' in *c2*). I inferior, L lateral, M medial, S superior. Scale bars = 50 μm for the neuron shape and 2 μm for the higher-magnification inserts (shown in *c2*). (Legend adapted and figure reprinted from Rasia-Filho et al. (2021) under CC BY license and Copyright © 2021 Rasia-Filho, Guerra, Vásquez, Dall'Oglio, Reberger, Jung, and Calcagnotto). (**c**) Three-dimensional reconstruction (using a supervised machine learning-based approach) of a thorny excrescence from the same neuron shown in (**a**). Note the convoluted form of this dendritic spine (arrows) and the multiple heads and stalks, from the original Golgi data (*a'*) to the final reconstruction and observation at different rotation angles (*b'-d'*). Images are from an adult individual. Scale bar = 2 μm

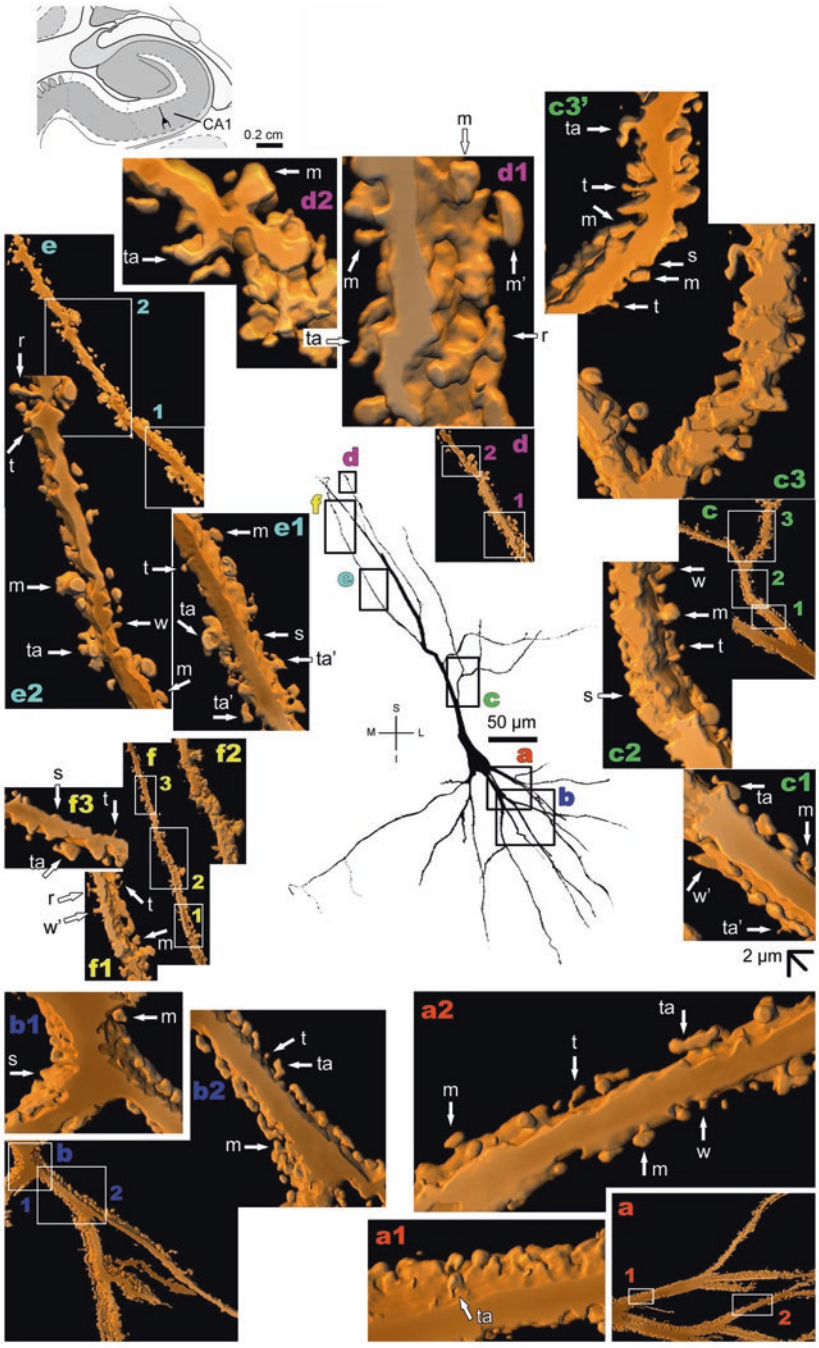

Fig. 9.14 Golgi-impregnated small pyramidal neuron from the human CA1 hippocampal region. (Top) Schematic diagram of a coronal section showing the human CA1 region, 22.6 mm posterior to the midpoint of the anterior commissure. (Adapted from Mai et al. (2008)). opt, optic tract. (Center) Two-dimensional reconstructed image illustrating the neuronal morphology under light microscopy. The distribution, density, and shape of three-dimensional-reconstructed dendritic spines are demonstrated in the inserts at higher magnification (**a**–**f**). Letters and numbers represent

synapses might be compartmentalizing the processing of information and what are the possibilities of coactivation and cooperativity between neighbor spines; (2) how distant synaptic inputs impact the function of other segments when signals are transmitted anterogradely along the dendritic tree and what is the resultant "code" elaborated from multiple activated sites; and (3) what is the balance between stable and plastic spines related to the need for processing new tasks and associating them with older ones within circuits and different brain areas. Considering that hippocampal spines are involved with memory formation, stable spines would serve as a common substrate for output activities that code this action. Otherwise, a certain percentage of spines should always be in a constant turnover to allow enough space in the membrane for processing new stimuli and determining the "weight" of these new inputs that occur every day along the lifespan (see a parallel discussion in Leopold et al. (2019)). It is also possible that small dendritic spines in these neurons would participate in long-term potentiation induction while large, thin, and mushroom spines would modulate different steps for long-term memory and circuitry plasticity (Matsuzaki et al. 2004; Bourne and Harris 2007; Kasai et al. 2010; Yuste 2013).

The turnover and functional implications of spines can be site- and task-specific. The dynamics of appearance and shrinkage of spines can be fast and in the order of minutes after activation in the hippocampus (Toni et al. 1999), but the loss of motor cortex spines many hours after inducing memory for a task impairs the execution of a learned behavior (Hayashi-Takagi et al. 2015). Then, the image of these spines likely represents the conjunct of spines needed to balance between the maintenance of long-lasting functional connections and the available synaptic sites with functional individuality to receive new, plastic network demands, keeping accurate integration of inputs and individual synaptic tuning. Such neuron is one among several others whose morphology and integrated function elaborate the memories and self-identity of each unique person. Interestingly, the principles controlling spine formation, retreat, or shape reconfiguration reflect how the adult brain remains adaptable and, with spines, has a capacity for experience-dependent alterations that seems "endless" (Leopold et al. 2019).

Cortical neurons are not randomly interconnected within the neuropil volume; rather, wiring specificity can result from the genetically defined identity of its constituents, morphological properties, electrical activity (Udvary et al. 2022), and activity- and circuitry-dependent features. It is then comprehensible why pyramidal

Fig. 9.14 (continued) sampled parts of the same dendritic segment (**a1**, **a2**, **b1**, **b2**, **c1**–**c3**, **d1**, **d2**, **e1**, **e2**, **f1**–**f3**). The apostrophe over the letters represents an image that was rotated in space after 3D reconstruction to show various pleomorphic dendritic spines (**c3'**). Note an intermediate to a high density of pleomorphic spines in the proximal segments of the basal (**a**, **b**) and apical (**c**) dendrites, which continue toward distal segments (**d**–**f**). Spines were classified as stubby (s), wide (w), thin (t), mushroom-like (m), ramified (r), or transitional/atypical ones (ta). Note the occurrence of spines with different shapes along the same dendritic segment, some relatively apart from the others (e.g., in **a2**, **e2**) or in groups (e.g., **b2**, **c3**, **d1**, **d2**). The presence of a spinule is indicated by the apostrophe attached to the corresponding spine (w' and ta' in **c1**, m' in **d1**, ta' in **e1**, and w' in **f1**). Images are from an adult individual. I inferior, L lateral, M medial, S superior. Scale bars = 50 μm for the neuron shape and 2 μm for the higher-magnification inserts (shown in **c1**). (Legend adapted and figure reprinted from Rasia-Filho et al. (2021) under CC BY license and Copyright © 2021 Rasia-Filho, Guerra, Vásquez, Dall'Oglio, Reberger, Jung, and Calcagnotto)

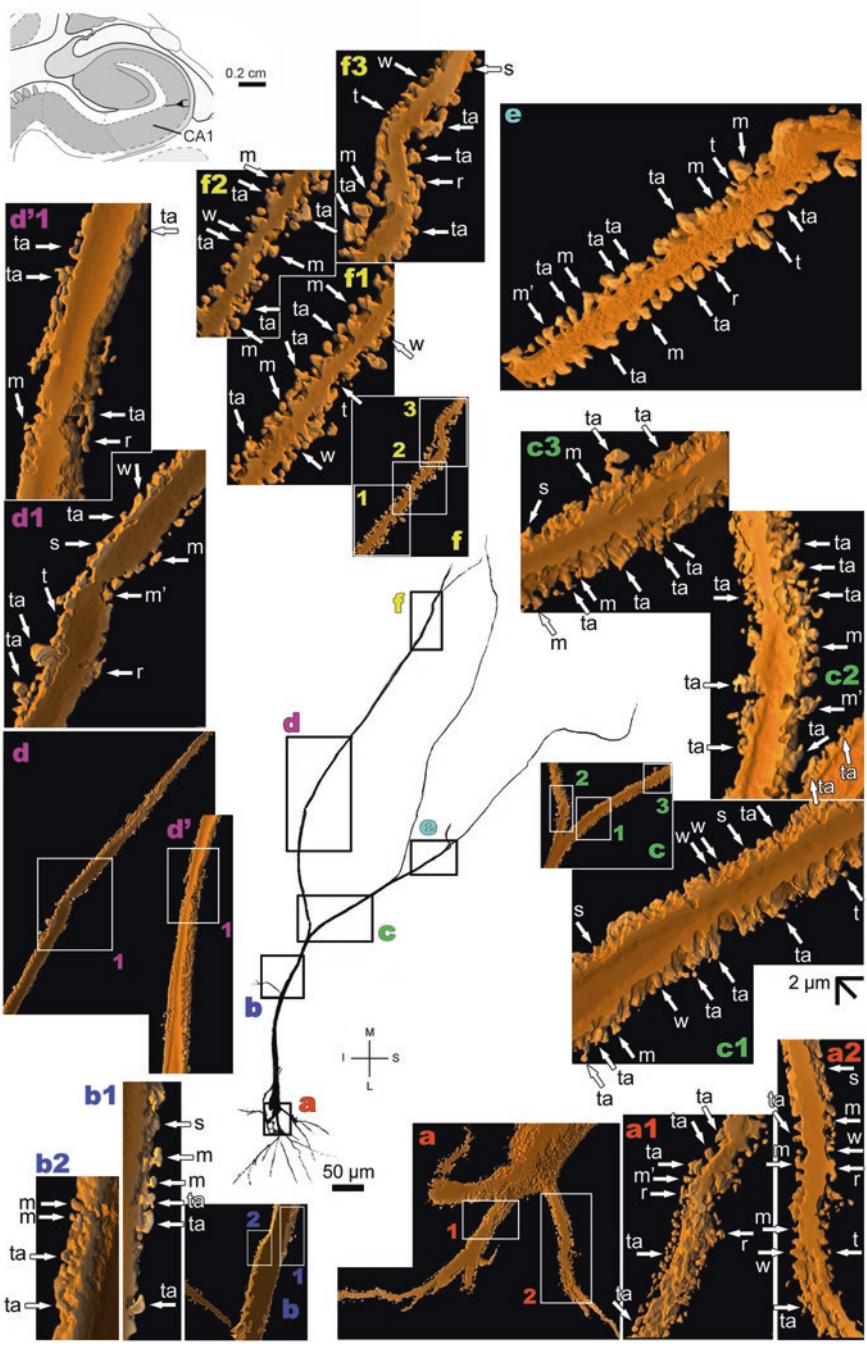

Fig. 9.15 Golgi-impregnated long pyramidal neuron from the human CA1 hippocampal region. (Top) Schematic diagram of a coronal section showing the human CA1 region, 22.6 mm posterior to the midpoint of the anterior commissure. (Adapted from Mai et al. (2008)). opt, optic

neurons vary in shape and properties within and between cortical areas, layers, and networks of different processing complexities (Moradi Chameh et al. 2021; Planert et al. 2021; Rasia-Filho et al. 2021). For example, pyramidal cell morphology shows interindividual variability and is not the same across the human anterior temporal lobe, as evidenced by different patterns of dendritic complexity and spine number (Benavides-Piccione et al. 2021). The greatest spine density was seen in the smallest and least complex layer III cells in the posterior temporal region T2c. On the other hand, neurons displaying the greatest size and high number of dendritic spines were found in the temporal pole. The estimated number of basal dendritic spines per distance from the soma showed a maximum number located around 90 μm, reaching a peak of approximately 1,000 spines, and an estimated total number of ~13,000 spines. Pyramidal cells in layer V were larger in size and number of spines (~ 1,200 spines at 110 μm and an estimated total number of 22,000 spines) than those in layer III in two individuals (Benavides-Piccione et al. 2021). An example of a Golgi-impregnated layer V long pyramidal neuron from the human temporal lobe is shown in Fig. 9.16. This cell has basal dendrites ramifying horizontally or directed to the adjacent layer VI, a long and straight apical dendrite with a main vertical shaft oriented to the superficial layers and some collateral branches. A moderate density of pleomorphic spines can be observed even in proximal segments of basal dendrites (Fig. 9.16a), whereas, in the apical dendrite, spines show a moderate-to-high density from proximal to intermediate segments (Fig. 9.16b, c) and a moderate density distally (Fig. 9.16d). Spines may show heterogeneous shapes and sizes along with the dendritic length, including various atypical/polymorphic forms (the 3D reconstruction of this layer V neocortical neuron is available as Supplementary Figures in Rasia-Filho et al. 2021).

Other neuron types compose the cortical cytoarchitecture and are found nearby large pyramidal neurons in layer V of higher-order human neocortical areas. An example is the "spindle-shaped" neuron in the posteromedial precuneus (PC) region (Fuentealba-Villaroel et al. 2022; Fig. 9.17). These cells are not so abundant and do

Fig. 9.15 (continued) tract. (Center) Two-dimensional reconstructed image illustrating the neuronal morphology under light microscopy. The distribution, density, and shape of three-dimensional-reconstructed dendritic spines are demonstrated in the inserts at higher magnification (**a**–**f**). Letters and numbers represent sampled parts of the same dendritic segment (**a1**, **a2**, **b1**, **b2**, **c1**–**c3**, **d1**, **f1**–**f3**). The apostrophe over the letters represents an image that was rotated in space after 3D reconstruction to show various pleomorphic dendritic spines (**d'**, **d'1**). Note the multitude of types and very high density of pleomorphic spines in the proximal segments of the basal dendrites (**a1**), moderate-to-high spine density in the proximal to intermediate segments of the apical dendrite (**b1**, **b2**), and very high density of spines in intermediate apical segments (**c1**–**c3**). Toward the distal parts of the apical dendritic branches, spines show an intermediate to high (**d1**, **d'1**, **e**) and a very high density of spines close to final shafts (**f1**–**f3**). Dendritic spines were classified as stubby (s), wide (w), thin (t), mushroom-like (m), ramified (r), or transitional/atypical ones (ta). Note that spines of different shapes and sizes coexist along the same dendritic segments (e.g., **a1**, **c1**–**c3**, **e**, **f1**–**f3**). The presence of a spinule is indicated by the apostrophe attached to the corresponding spine (m' in **a1**, **d1**, **e**). Images are from an adult individual. I inferior, L lateral, M medial, S superior. Scale bars = 50 μm for the neuron shape and 2 μm for the higher-magnification inserts (shown in **c1**). (Legend adapted and figure reprinted from Rasia-Filho et al. (2021) under CC BY license and Copyright © 2021 Rasia-Filho, Guerra, Vásquez, Dall'Oglio, Reberger, Jung, and Calcagnotto)

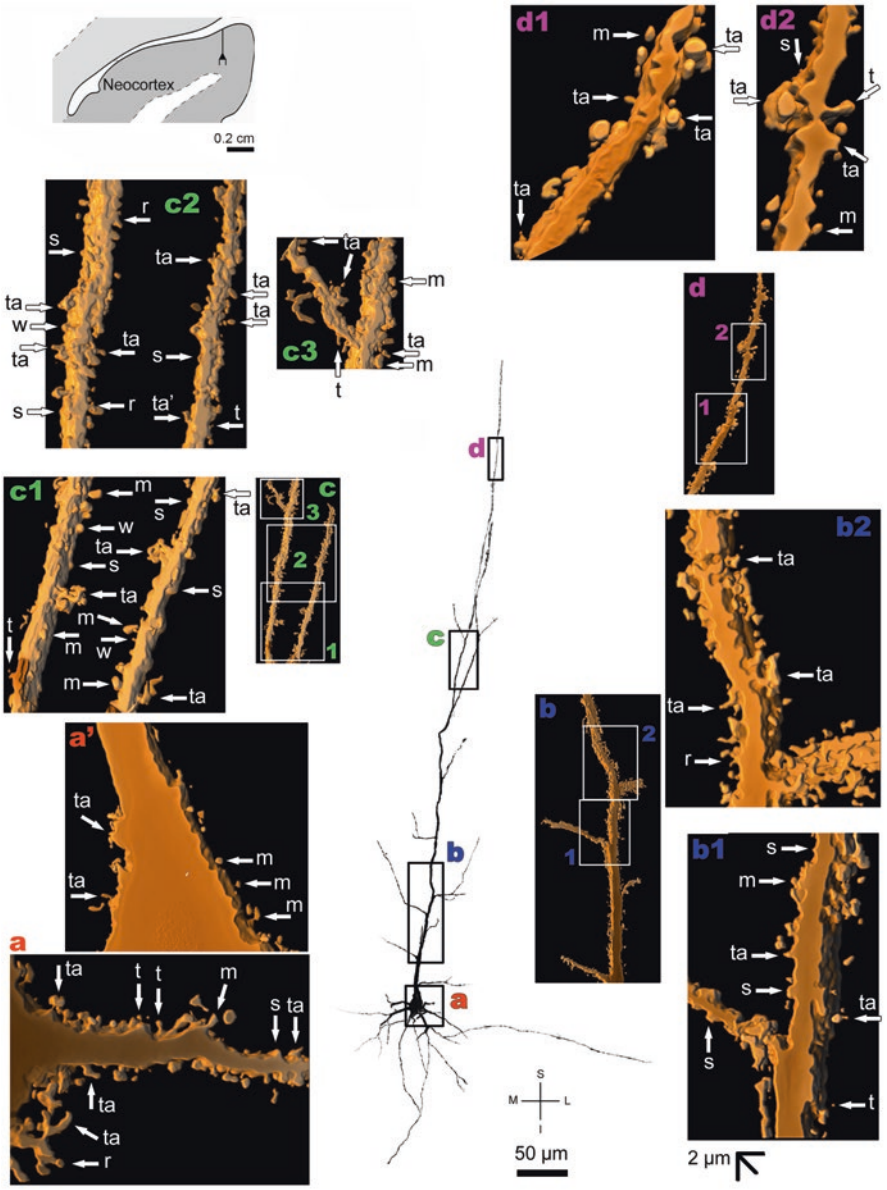

Fig. 9.16 Golgi-impregnated large pyramidal neuron from layer V of the human anterolateral temporal lobe. (Top) Schematic diagram of a coronal section showing the corresponding neocortical region, 9.3 mm posterior to the midpoint of the anterior commissure. (Adapted from Mai et al. (2008)). opt, optic tract. (Center) Two-dimensional reconstructed image illustrating the neuronal morphology under light microscopy. The distribution, density, and shape of 3D-reconstructed dendritic spines are demonstrated in the inserts at higher magnification (**a–d**). Letters and numbers represent sampled parts of the same dendritic segments (**b1**, **b2**, **c1–c3**, **d1**, **d2**). The apostrophe (in **a'**) represents an image that was rotated in space after 3D reconstruction to show various somatic

not have the same morphology compared to pyramidal ones. Spiny spindle-shaped cells were found in layer V merging with layer VI in the PC of adult humans and have a characteristic vertical, elongated cell body, two main longitudinally oriented ascending and descending dendrites with varied branching aspect and radial orientation. Pleomorphic spines with a sparse to moderate density cover proximal to distal segments. Some spines show atypical/polymorphic forms, including convoluted shapes with different neck thicknesses and/or multiple bulbous structures (Fig. 9.17f2 right). Other cells in the same location display a similar cell body shape, straight dendritic shafts devoid of main ramifications in both ascending and descending branches, a moderate density of small dendritic spines, or few spines along the dendritic shafts (Fuentealba-Villaroel et al. 2022). There are no electrophysiological recordings or transcriptomic profile studies of these cells currently, but it is likely that these cells also participate in higher-order neural processing circuitries involving the PC. For example, the human PC modulates sensorimotor, visual, cognitive/associative information, episodic memory retrieval, consciousness, self-centered mental imagery, and empathy (Cavanna 2007; Margulies et al. 2009, 2016; Zebarjadi et al. 2021; Lyu et al. 2023; see also Messina et al. 2023). However, based on their distinct dendritic shape, spindle-shaped neurons probably process synaptic inputs in distinct ways than the adjacent pyramidal cells.

The cell body shape and the display of longitudinal primary dendrites at opposite somatic poles of "spindle-shaped" neurons in the human PC are intriguing. That is because they resemble the general somatic and primary dendrites' shape of layer V von Economo neurons (VENs) from the human ACC (Fig. 9.18; see a critical discussion in Banovac et al. 2019, 2021 and Fuentealba-Villaroel et al. 2022), and both the PC and the ACC can be part of a general intelligence circuit (Bruton 2021). In this regard, the human VENs have been described in restricted cortical areas with some features that are not similar to layer V pyramidal neurons. VENs have phylogenetic, ontogenetic, immunohistochemical, and electrophysiological particularities as well as a vulnerability in diseases with social and emotional deficits (Allman et al. 2005, 2010, 2011a, b; Stimpson et al. 2011; Raghanti et al. 2015; Cobos and Seeley 2015; Dijkstra et al. 2018; Jacot-Descombes et al. 2020; see also Yang et al. 2019 and Hodge et al. 2020 for transcriptomic data). For example, VENs are more numerous in the ACC and frontoinsular cortex of humans than in apes (Allman et al. 2010). VENs are rarely seen during gestation (i.e., VENs are not identified morphologically until gestational week 36), but their number increases during the first

Fig. 9.16 (continued) and dendritic spines. Note the moderate density of pleomorphic spines in the proximal segments of the basal dendrites (**a**) and along the apical dendrite (**b1**). Moderate-to-high density of dendritic spines is observed toward intermediate (**b2**) to distal (**c1**–**c3**) segments of the apical dendrite. Moderate spine density is observed at distal apical dendritic segments (**d1**, **d2**). Some spines were observed in the cell body (**a'**). Dendritic spines were classified as stubby (s), wide (w), thin (t), mushroom-like (m), ramified (r), or transitional/atypical ones (ta). Dendritic spines of very different shapes and sizes coexist along the same dendritic segments (e.g., **a**, **b2**, **c1**, **d1**). Images are from an adult individual. I inferior, L lateral, M medial, S superior. Scale bars = 50 μm for the neuron shape and 2 μm for the higher-magnification inserts (shown in **b1**). (Legend adapted and figure reprinted from Rasia-Filho et al. (2021) under CC BY license and Copyright © 2021 Rasia-Filho, Guerra, Vásquez, Dall'Oglio, Reberger, Jung, and Calcagnotto)

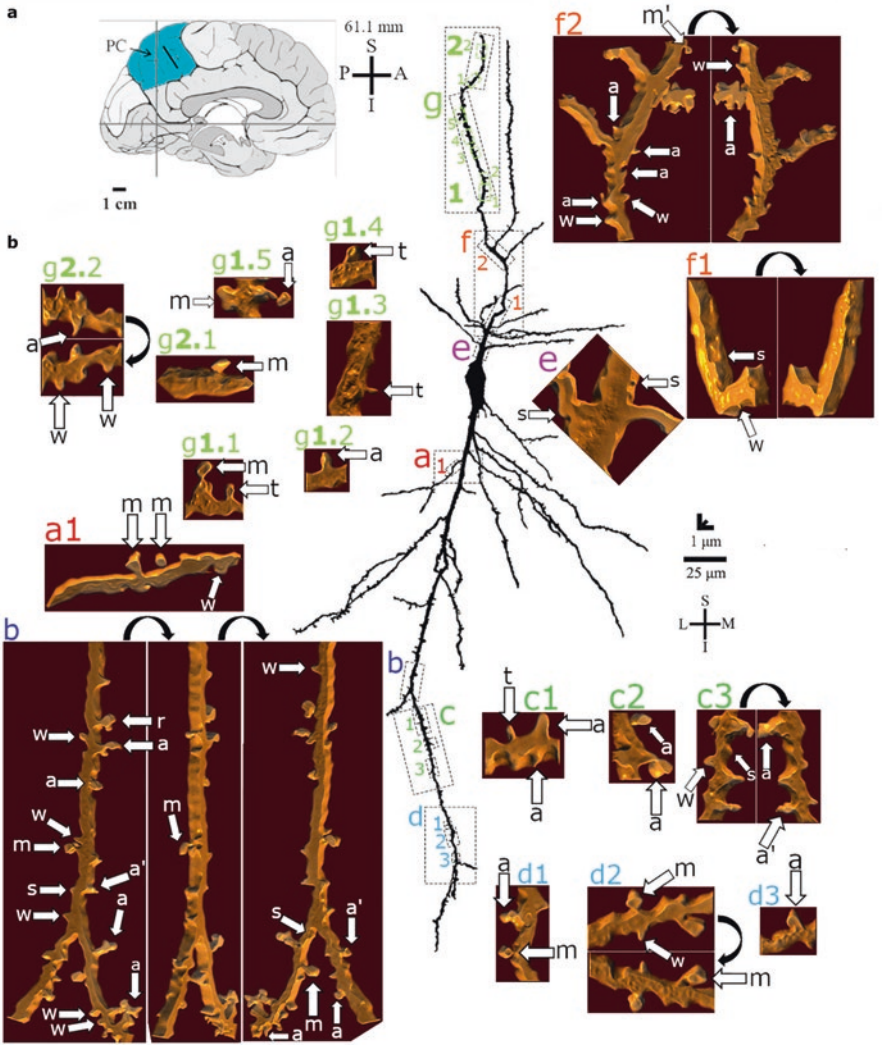

Fig. 9.17 Golgi-impregnated spindle-shaped neuron from layer V in transition to layer VI in the human precuneus (central region), part of the posteromedial cerebral cortex. (Top) Schematic diagram of a coronal section showing the corresponding neocortical region, 61.1 mm posterior to the midpoint of the anterior commissure. (Adapted from Mai et al. (2008, 2016)). opt, optic tract. (Center) Two-dimensional reconstructed image illustrating the neuronal morphology under light microscopy. The distribution, density, and shape of 3D-reconstructed dendritic spines are demonstrated in the inserts at higher magnification (**a**–**g**). Letters, numbers, and subdivisions represent sampled parts of the same dendritic segment (**c1-3**, **d1-3**, **f1-2**, **g1.1**-**2.2**). Curved arrows indicate that the 3D reconstructed images were rotated and are shown at different observation angles (**b**, **c3**, **d2**, **f1**, **f2**, **g2.2**). Note the distribution of a low-to-moderate density of pleomorphic spines along the dendritic segments. Spines were classified as stubby (s), wide (w), thin (t), mushroom (m), ramified (r), with a transitional (t), or atypical aspect (a). The presence of a spinule is indicated by the apostrophe attached to the corresponding spine (a' in **b** and **c3**). Images are from an adult individual. I inferior, L lateral, M medial, S superior. Scale bars = 25 µm for the neuron shape and 1 µm for the inserts. (Legend adapted and figure reprinted from Fuentealba-Villarroel et al. (2022) under CC BY license and Copyright © 2022 Fuentealba-Villarroel, Renner, Hilbig, Bruton, and Rasia-Filho)

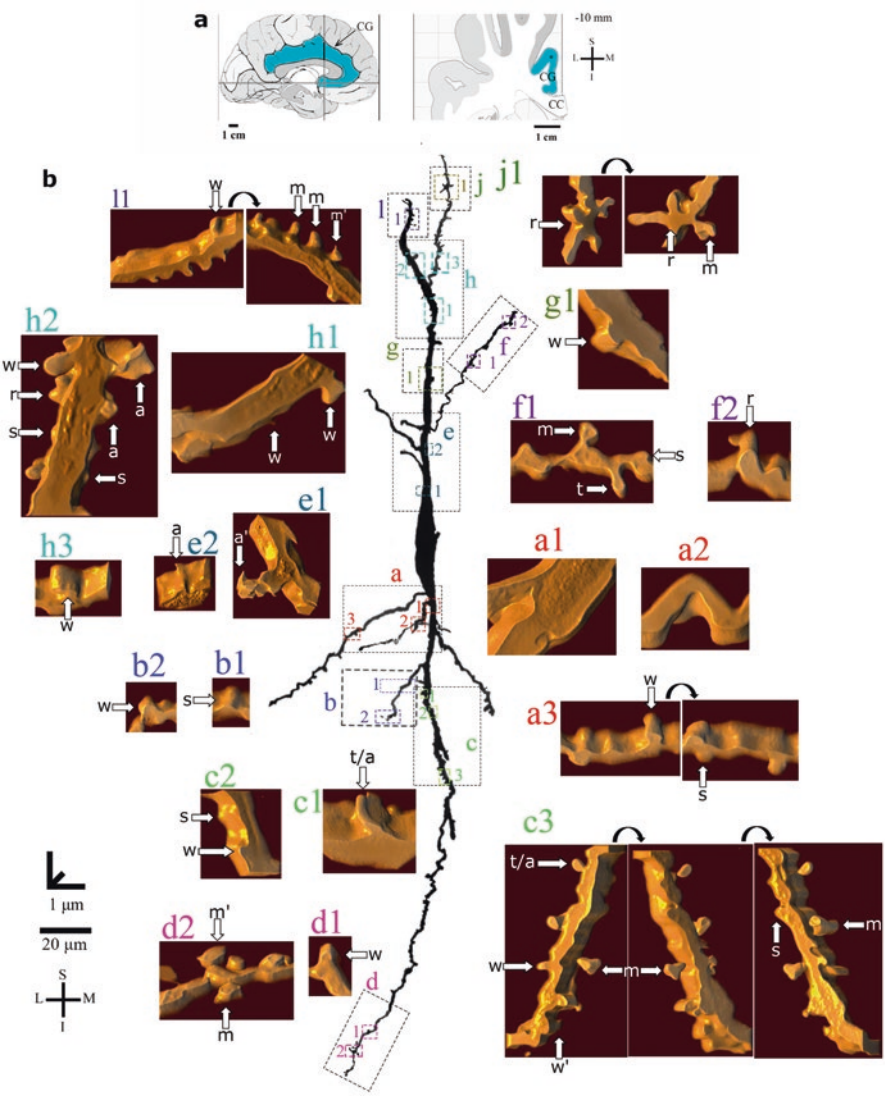

Fig. 9.18 Golgi-impregnated von Economo neuron from layer V in the human cingulate cortex. (Top) Schematic diagram of a coronal section showing the corresponding neocortical region, 10 mm anterior to the midpoint of the anterior commissure. (Adapted from Mai et al. 2008). opt, optic tract. (Center) Two-dimensional reconstructed image illustrating the neuronal morphology under light microscopy. The distribution, density, and shape of 3D-reconstructed dendritic spines are demonstrated in the inserts at higher magnification (**a–l**). Letters, numbers, and subdivisions represent sample parts of the same dendritic segment (**a1-3**, **b1**, **b2**, **c1-3**, **d1**, **d2**, **e1**, **e2**, **f1**, **f2**, **h1-3**). Curved arrows indicate that the 3D reconstructed images were rotated and are shown at different observation angles (**a3**, **c3**, **j1**, **l1**). Note the intermediate density of spines along the dendritic length, but the variety of spine shapes in main descending and ascending shafts and collaterals. Spines were classified as stubby (s), wide (w), thin (t), mushroom (m), ramified (r), with a transitional (t/), or atypical aspect (a). The presence of a spinule is indicated by the apostrophe attached to the corresponding spine (w' in **c3**, m' in **d2**, a' in **e1**, m' in **l1**). Images are from an adult individual. I inferior, L lateral, M medial, S superior. Scale bars = 20 µm for the neuron shape and 1 µm for the inserts. (Legend adapted and figure reprinted from Correa-Júnior et al (2020) under CC BY license and Copyright © 2020 Correa-Júnior, Renner, Fuentealba-Villarroel, Hilbig, and Rasia-Filho)

8 months after birth, decrease afterward, and reach stable values at 4–8 years (Allman et al. 2010, 2011a). The number of VENs remains constant along the lifespan in individuals with average cognition, and a higher density of VENs exists in the ACC of individuals (≥age 80) who show outstanding memory abilities (Gefen et al. 2015). Based on transcriptomic data, human VENs may be projecting cells to extratelencephalic, subcortical targets (Hodge et al. 2020), whereas, in gorillas, VENs also project to the inferior frontal gyrus, inferotemporal cortex, hippocampus, septum, and amygdala (Allman et al. 2010). VENs may also innervate the midbrain periaqueductal gray and the parabrachial nucleus of monkeys (discussed in Evrard et al. 2012), likely associating cortical processing with emotions and the control of sympathetic/parasympathetic sites in the brainstem and spinal cord (Cobos and Seeley 2015; Jacot-Descombes et al. 2020).

The human ACC VENs were reported in a morphological *continuum* from sparsely branched (Watson et al. 2006) to more extensively ramified cells with varied collateral branches with distinct distribution, density, and shape of dendritic spines (Correa-Júnior et al. 2020). VENs can display a brush-like aspect for the descending dendrites from where emerges an axon (Banovac et al. 2019, depicted in layer V of a 1-month-old human infant insular cortex by Cajal (1909–1911) and shown in Banovac et al. (2021)). If VENs show more or less branched ascending and descending dendrites, these morphological features imply a higher surface for synaptic processing and plasticity modulated by pleomorphic spines within an extended neuropil volume. Furthermore, the firing output of VENs would be affected by a selective location of the axon along the dendritic architecture (Banovac et al. 2019, 2021). Jointly with some particular intrinsic properties of putative VENs' membrane (as described in the human frontoinsular cortex, Hodge et al. 2020), the heterogeneity of dendritic arbor ramification and spine number suggest a heterogeneous capacity between VENs for input sampling, computational power, and elaboration of output codes as projection neurons (Correa-Júnior et al. 2020; 3D reconstruction of human PC and ACC neurons are available as Supplementary Figures in Fuentealba-Villarroel et al. 2022 and Correa-Júnior et al. 2020, respectively).

In addition, the human cingulate cortex (from 62- to 91-year-old individuals) shows large pyramidal cells of Betz located in layer Vb of the primitive gigantopyramidal field at the bottom of the cingulate sulcus (Braak and Braak 1976). These Golgi-impregnated cells have a pyramidal or pear-shaped cell body, short and slender (sometimes thick) branched basal dendrites, a varied number of dendrites emerging from the lateral surface of the soma, and a moderate number of spines with "thread-Iike stems and rounded knobs." Spines are evenly distributed along the whole length of the dendrite. Proximal parts of dendrites are covered with spiny appendages, the soma is often covered with a small number of spiny projections with large rounded knobs, and the thick main shaft has numerous spines at proximal segments, which continues with "numerous long-stalked, bent, and twisted spines closely spaced together." At most distal parts, the apical dendrite bifurcates repeatedly. These dendrites have "sessile and stalked spines ending in a knob" and occasionally "small clusters of spines may be followed by short zones almost devoid of spiny projections" (Braak and Braak 1976; see also the description and images of dendrites with a high density of pleomorphic spines of Betz cells in the human precentral gigantopyramidal field in this same work).

Together, the cingulate cortex microcircuits exemplify how coexisting different types of neurons with discrepant proportions can integrate multimodal inputs and elaborate coherent output displays. The cingulate cortex is an interesting part of the "proisocortex" in the paralimbic cortex, a phylogenetically older part compared to the neocortex (Braak 1979; Pandya et al. 2015; Kolb and Whishaw 2021). However, it is much more than a primitive stage of cortical evolution and comprises neural networks for high-order attentional processes/executive functions with sensory processing, flexible control of the motor, and affective information for goal-directed and exploratory behavior within complex social interactions (Allman et al. 2001; Vogt 2015; Medalla et al. 2022). The human cingulate cortex elaborates cognition and premotor planning with motivational features, social awareness, and emotions such as love, trust, empathy, deception, guilt, and fear, as well as evokes heart rate and arterial pressure, respiratory, and gastrointestinal responses (Allman et al. 2001, 2010, 2011a; Watson et al. 2006; Xuan et al. 2016 and references therein).

It is also noteworthy that morphologically and biophysically distinct pyramidal neurons in the ACC project to the dorsal premotor cortex and the amygdaloid nuclei in rhesus monkeys. Layer V pyramidal cells projecting to amygdaloid nuclei show greater excitability, apical dendritic complexity, spine densities, and diversity of inhibitory inputs than those targeting the dorsal premotor cortex (Medalla et al. 2022). The projecting neurons in the ACC also stimulate two pathways simultaneously to generate human speech: one via PAG for vocalization and another via Broca´s area to convert vocalization into words and sentences (Holstege and Subramanian 2016).

9.5 Human Spine Features Revealed by Further Microscopic Techniques

Besides the "classic" Golgi-impregnation procedure mentioned above, other methodological approaches corroborated and expanded the study of dendritic spines in humans (see also Chap. 2 in this book). One of them is the use of DiI, a fluorescent dye of the carbocyanine family, under confocal microscopy. Fine-powdered dye DiI extracellularly diffuses over intact cellular membranes and reveals fine 3D features of dendritic spine morphology. Spine connectivity can be assessed when associated with immunohistochemical markers for presynaptic proteins, such as synaptophysin (Kim et al. 2007; Rasia-Filho et al. 2010). Confocal images using DiI dye allow the visualization of human MeA dendritic spines with varied stubby/wide, thin, mushroom, ramified, or intermediate/atypical forms within a *continuum* of sizes, either isolated or grouped, and from proximal to distal dendritic branches (Fig. 9.19). Large and thin spines with a gemmule appearance and filopodium found in this brain area suggest additional possibilities for spinogenesis in adult individuals (Dall'Oglio et al. 2015; Fig. 9.19f).

The variety of heterogeneous spines in the human MeA includes thin spines (Fig. 9.19a) and stubby/wide spines (Fig. 9.19b) ranging from small to relatively large forms. The head sizes of mushroom spines can also vary and display a large and flat appearance (Fig. 9.19c, first to sixth images) or irregular surface (Fig. 9.19c, last image). Ramified spines show a single large stalk branching into two heads

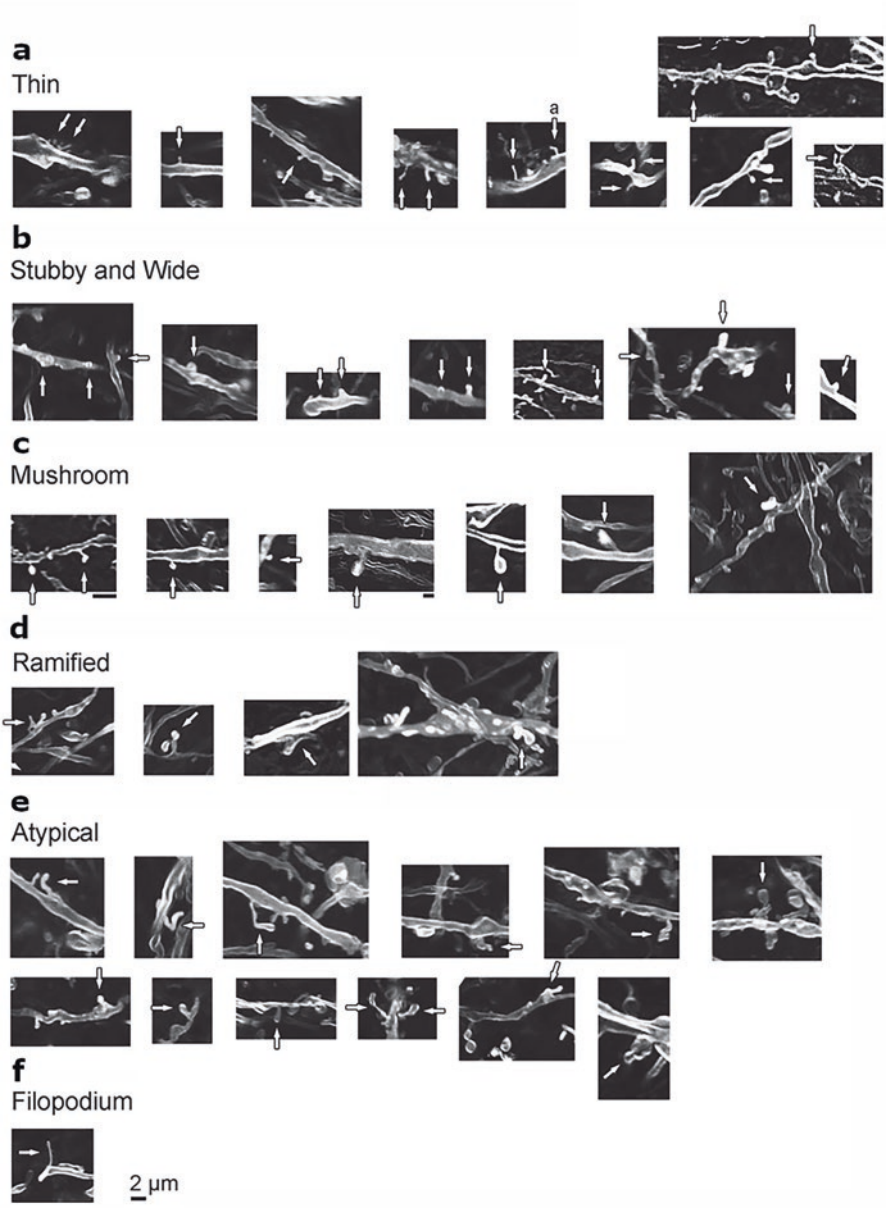

Fig. 9.19 Three-dimensional reconstructed fluorescent confocal microscopy image (using extracellularly applied DiI dye) of dendritic spines from the human medial amygdaloid nucleus. Differently shaped spines (arrows) were classified as (**a**) thin, (**b**) stubby/wide, (**c**) mushroom, (**d**) ramified, and (**e**) transitional or atypical forms. Note the varied shapes and sizes within each spine class. (**f**) A filopodium is also shown with an elongated neck and no evident head. Images are from an adult individual. Scale bar = 2 µm. (Legend adapted and figure reprinted from Dall'Oglio et al. (2015) under CCC RightsLink® license #5385561144316, originally published by John Wiley & Sons, Inc)

(Fig. 9.19d, first and second images), a single stalk giving rise to a branch with no identified spine head (Fig. 9.19d, third image), or a large stalk and separated heads (Fig. 9.19d, last image). Some transitional/atypical spines (Fig. 9.19e) might be intermediate forms of previously classified spines, considering the combination of the length and thickness of the spine neck and the size and shape of the spine head (Fig. 9.19e, first to third images in the second row). Other atypical/polymorphic spines include the following: (1) double spine (Fig. 9.19a, fifth image, marked "a"); (2) spines with a single, large, elongated, and thick protrusion (Fig. 9.19e, first and second images in the first row); (3) spines with an enlarged finger-like neck and a fusiform head (Fig. 9.19e, third image in the first row); (4) spines with curved or "twisted" endings (Fig. 9.19e, fourth and fifth images in the first row); (5) branched spine with various bulbous protrusions (Fig. 9.19e, last image in the second row); (6) large spine resembling a simple racemose aspect (Fig. 9.19e, last image in the first row); (7) spines with a thin, elongated neck resembling a gemmule aspect with an atypical elongated head (Fig. 9.19e, fourth image in the second row, left); (8) spines with a single bulbous protrusion giving rise to small protruding heads attached to a thick "neck" (Fig. 9.19e, fifth image in the second row); and (9) thorny excrescence with lobed protrusions (Fig. 9.19e, last image in the second row; descriptions based on Fiala and Harris 1999). The synaptic relevance for some of these spines was revealed by transmission electron microscopy (TEM, described below).

Likewise, intracellular injection of Lucifer Yellow allowed 3D reconstructions (Figs. 9.20a and 9.21) and quantifiable morphological data for supragranular pyramidal dendrites and spines of the adult human cingulate cortex, CA1 hippocampal field, and temporal cortex (Benavides-Piccione et al. 2013; Eyal et al. 2018; Benavides-Piccione et al. 2020, 2021). Using *postmortem* human brains from two men (aged 40 and 85), 3D fluorescent images under confocal microscopy revealed the dendritic spine density of layer III pyramidal neurons of the human anterior cingulate gyrus (Benavides-Piccione et al. 2013). Accordingly, pleomorphic spines were found along the dendritic length of both basal (Fig. 9.20b, note the lack of spines in the proximal segment) and apical (Fig. 9.20c, 100 μm away from the soma) shafts, with no variation in spine morphologies related to distance from the soma, but with smaller spines in basal dendrites than in the apical one. On the other hand, there is a high mean density of spines in apical dendrites than in basal dendrites. In the basal dendrite of the younger person, dendritic spine density reached a maximum of approximately 1.9 spines/μm at a 110-μm distance from the soma and then slightly decreased distally. In the apical dendrite, spine density increased to a maximum of 4.3 spines/μm at a 160-μm distance from the soma (Benavides-Piccione et al. 2013).

This same procedure unraveled the heterogeneity in the dendritic arbor of pyramidal neurons in the CA1 field of the adult human hippocampal formation, which is more complex than in rats (Benavides-Piccione et al. 2020; Fig. 9.4a). Examples of reconstructed fluorescent dendritic spines of layer III pyramidal cells from the human temporal cortex (Brodmann's area 20) are shown in Fig. 9.21. These are the spiny neurons identified with morphological, biophysical, and computational

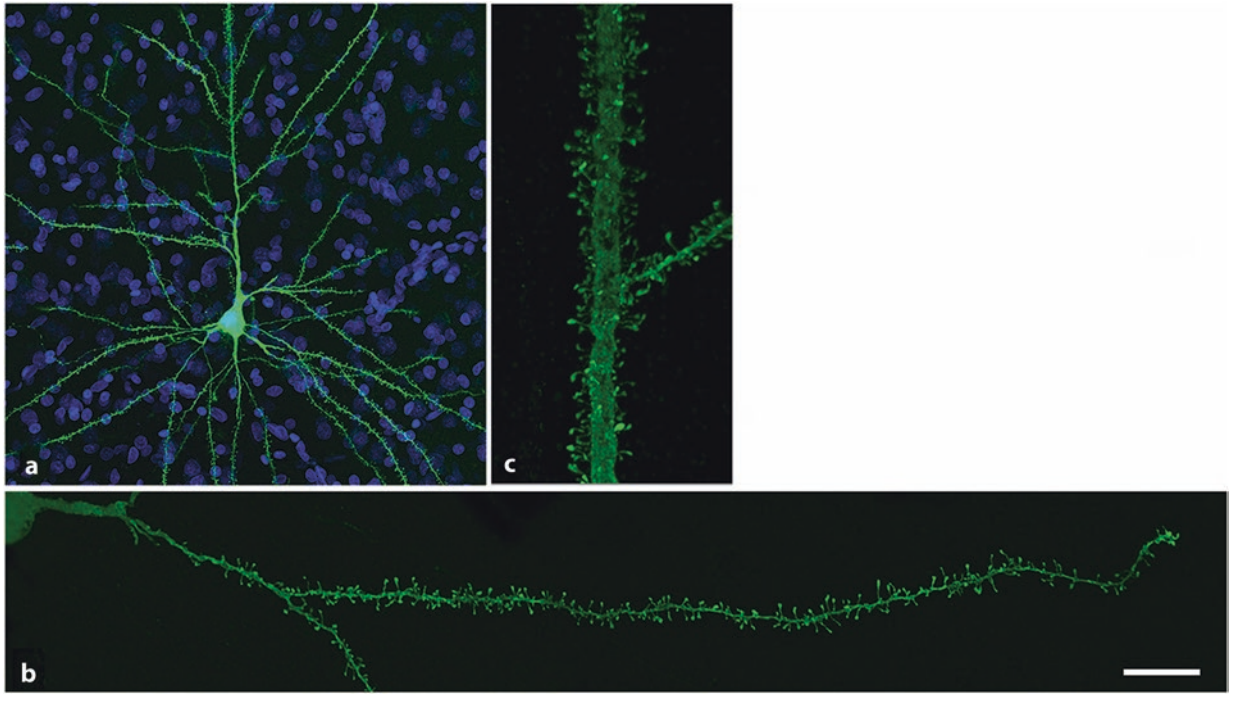

Fig. 9.20 (**a**) Confocal microscopy image "z" projection of a pyramidal neuron (injected with Lucifer Yellow) located in layer III of the adult human cingulate cortex. DAPI staining (in blue) identifies cell bodies. High-magnification images are provided for (**b**) a ramified basal dendrite and (**c**) an apical dendritic segment. In (**b**), note virtually no spines at the first proximal micrometers (left), the progressive increase of pleomorphic spines along intermediate parts (center), and spines remaining visible at distal segments (right). In (**c**), note the density of spines covering the main apical dendritic shaft (100 μm away from the soma) as well as along the collateral branch. Scale bar = 40 μm in (**a**); 13 μm in (**b**); and 7 μm in (**c**). (Legend adapted and figure reprinted from Benavides-Piccione et al. (2013) under CCC RightsLink® license #5385651024769, originally published by Oxford University Press)

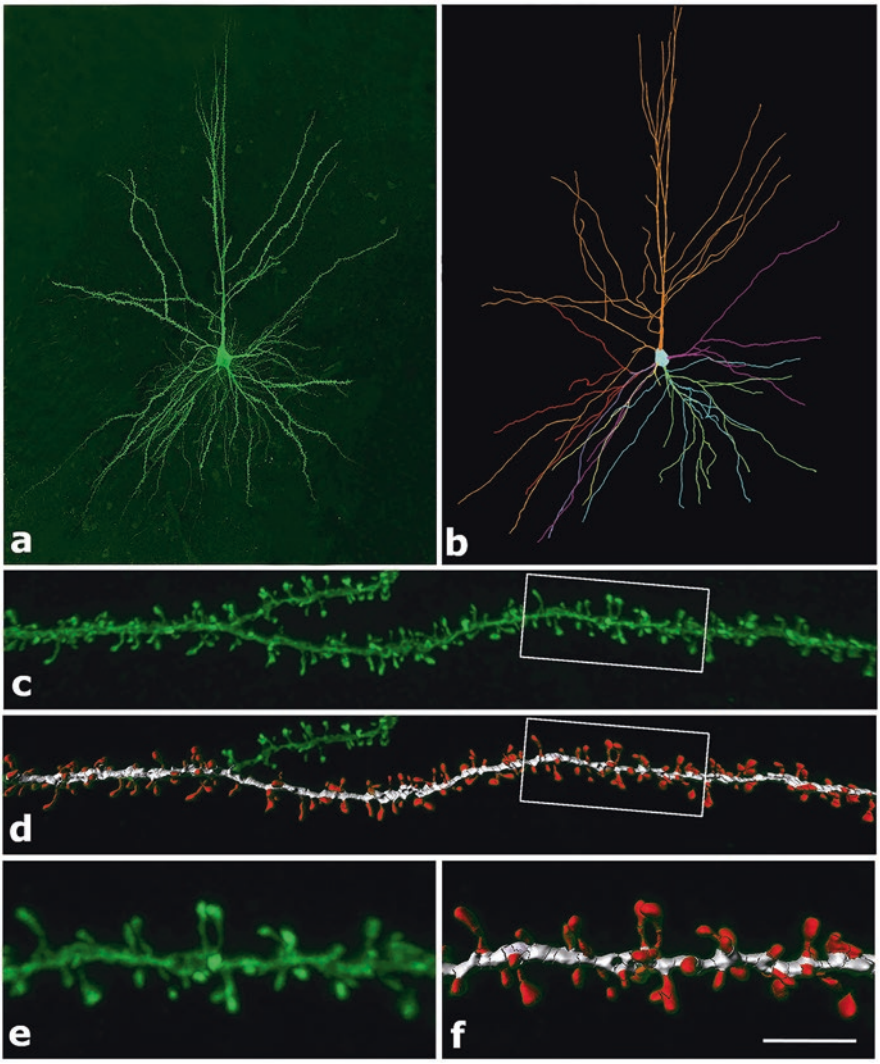

Fig. 9.21 (**a**) Confocal microscopy image "z" projection of a pyramidal neuron (injected with Lucifer Yellow) located in layer III of the human temporal cortex. (**b**) Three-dimensional reconstruction of the neuron shown in (**a**) showing the apical dendritic arbor in orange and the varied basal dendritic arborization with other colors. (**c**) Confocal microscopy image showing a horizontally projecting labeled spiny basal dendrite. (**d**) Reconstructed dendritic spines (red) and dendritic shaft (white). (**e**, **f**) Higher-magnification images of the dendritic segment are indicated by boxed areas in (**c**) and (**d**). Note the presence and distribution of intermingled pleomorphic spines, some with long and thin shapes. Scale bar = 110 μm (in **a** and **b**), 10 μm (in **c** and **d**), and 4.5 μm (in **e** and **f**). (Legend adapted and figure reprinted from Eyal et al. (2018) under CC BY license and Copyright © 2018 Eyal, Verhoog, Testa-Silva, Deitcher, Benavides-Piccione, DeFelipe, de Kock, Mansvelder, and Segev)

distinct properties in our species (Eyal et al. 2018). The morphology of Lucifer Yellow injected pyramidal neurons was studied in layers IIIa and Vb of the anterolateral middle and inferior temporal gyri (Brodmann's areas 20, 21, and 38) from patients neurosurgically treated for pharmacoresistant temporal lobe epilepsy (Benavides-Piccione et al. 2021). Findings suggest a relationship between dendritic branching and the number of spines likely aiming for balanced neuronal excitability (Benavides-Piccione et al. 2021). Moreover, data reinforce that differences in dendritic structure and density of spines are regulated at every single cell, brain area, and person, providing a high degree of possible arrays and probabilistic possibilities of functioning for each component of neural circuits, for information processing demands, and flexible, adaptable responses to new conditions.

9.5.1 Topology and Ultrastructure of Human Dendritic Spines

Another relevant issue is whether dendritic spines emerge isolated or grouped for synaptic purposes. Spines were already reported to form functional clusters within micrometers along the dendritic segment (Lu and Zuo 2017; Kastellakis and Poirazi 2019), and clustered synaptic modifications facilitate dendritic computation in learning and memory (Ma and Zuo 2022). For example, the apical terminal dendrites of layer III pyramidal neurons of the monkey prefrontal cortex display spatially (nonrandom) clusters of mushroom and stubby spines (Yadav et al. 2012). "The clustering of synapses may emerge from synapses receiving similar input, or via many processes that allow for crosstalk between nearby synapses within a dendritic branch, leading to cooperative plasticity. Clustered synapses can act in concert to exploit maximally the nonlinear integration potential of the dendritic branches in which they reside. Their main contribution is to facilitate the induction of dendritic spikes and dendritic plateau potentials, which provide advanced computational and memory-related capabilities to dendrites and single neurons" (Kastellakis and Poirazi 2019). As will be mentioned in the following section, some human spines can be lost in clusters in Alzheimer's disease (Mijalkov et al. 2021).

On the other hand, when synaptic wiring is random, the dimension of a representation formed by many sparsely connected neurons can be higher than that of a smaller number of densely connected elements (Litwin-Kumar et al. 2017). If this possibility is adapted to dendritic spines, multiple connections in different spines along dendrites would provide a high-dimensional representation and output pattern to different ensembles of inputs. It is also possible that both clustered and scattered random contacts can occur on dendrites, allowing different but complementary strategies for the dendritic integration of information. Providing more alternatives for the dendritic mechanisms recruited for postsynaptic summation might give an exceptional repertoire for spiny dendritic segments associate signals linearly and nonlinearly and modulate cellular excitability (Tran-Van-Minh et al. 2015).

Dendritic spines with a helical topology means that spines are distributed in regular linear arrays on the shaft perimeter, even though helixes would show no particular rotational preference (Yuste 2010). Helical spine ordering was observed in distal dendrites of cerebellar Purkinje cells of fish and mice (O´Brien and Unwin 2006). Such short-pitch helical paths would maximize the chance for different spines to interact with different passing axons and facilitate synaptic interactions (O´Brien and Unwin 2006). The existence of a similar pattern was tested in 3D reconstructed apical and basal spiny dendrites of layer III pyramidal neurons from the frontal, temporal, and cingulate cortex in humans (40 and 85 years, Morales et al. 2014). Using Fourier and spatial statistical analyses of spine insertion points, some evidence for helical patterns was present in a minority of samples. Nevertheless, most spines followed a random positioning principle and did not show a helical pattern in apical or basal dendrites or among spines of different volumes and lengths in these human samples (Morales et al. 2014; Fig. 9.22).

Finally, TEM and additional modern techniques revealed the fine-tuned synaptic processing that reflects the complexity of dendritic and spine structural and functional organization in humans. As mentioned above, human synapses can show unique properties and synaptic heterogeneities can occur in cortical and subcortical areas related to cellular specializations and circuits. Some basic principles can be found, but particular arrangements imply the "role" of each synapse and its integration in each cell. For example, the synaptic organization of the human temporal lobe neocortex was recently reported using high-resolution transmission, focused ion beam scanning, and electron microscopic tomography (Rollenhagen et al. 2020). This approach provided quantitative 3D models of synapses (overall geometry, number, size, shape of active zones, and synaptic vesicles) and insights into the morphological correlates of layer-specifically organized synaptic transmission and plasticity in the human neocortex (Rollenhagen et al. 2020; see additional data in this reference).

Ultrastructural data from human MeA neurons also demonstrated how common and particular features coexist in the synaptic organization of a brain area. Axonal synaptic contacts can form asymmetric and symmetric contacts directly on dendritic shafts and on differently shaped spines (Dall'Oglio et al. 2015; Figs. 9.23 and 9.24). Axon terminals formed isolated (Fig. 9.23a) or multiple asymmetric contacts (Fig. 9.23b), and the presynaptic terminals of asymmetric synapses contained round, small, electron-lucent vesicles (e.g., Fig. 9.23a, c, d) whereas symmetric presynaptic terminals exhibited small or pleomorphic vesicles, some intermingled with large, dense-core vesicles (e.g., Fig. 9.23e, g, top).

Dendritic spines of different shapes and sizes showed axospinous monosynaptic or, in some cases, multisynaptic sites with contacts located at the spine head and neck (Fig. 9.23f–m). These synapses were usually of the asymmetric type (e.g., Fig. 9.23f, h). Spines could also form axospinous symmetric contacts (e.g., Fig. 9.23e). Synaptic terminals contacted different parts of stubby/wide spines (e.g., at the base, Fig. 9.23c; at the upper part, Fig. 9.23d; or at the lateral part of the spine,

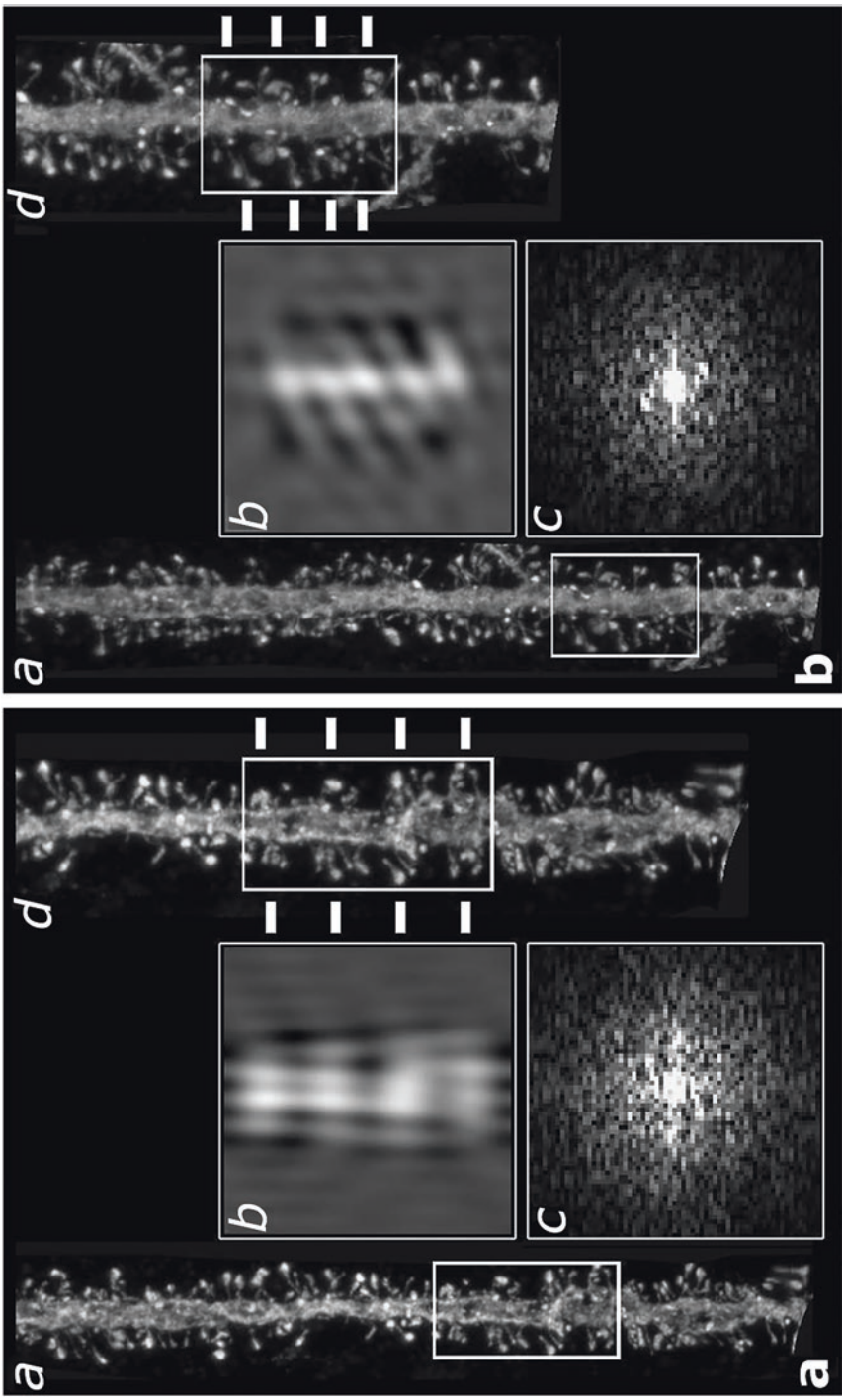

Fig. 9.22 Helical or random positions of dendritic spines were tested using confocal microscopy images of Lucifer Yellow injected pyramidal neurons from layer III of the adult human frontal, temporal, and cingulate cortex. Fourier analysis and spatial statistics were used to analyze spine position along the apical and basal

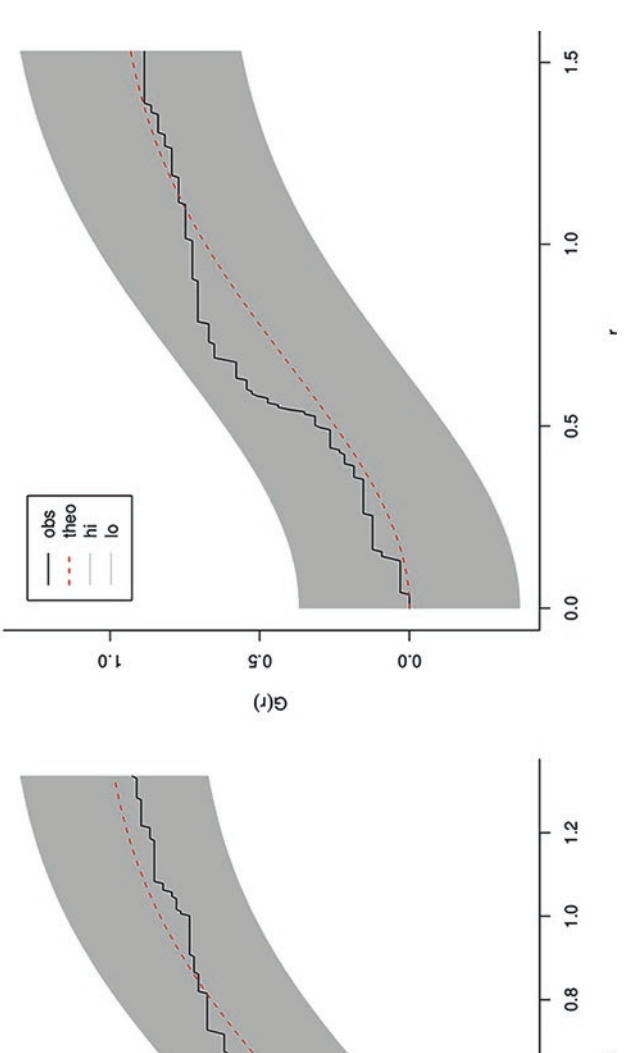

Fig. 9.122 (continued) dendrites. (**a**, **b**) "Two examples of dendritic segments from apical dendrites (**a**), showing regions in which helical distributions were apparent (white boxed areas) after the corresponding Fourier and inverse Fourier transforms (**b**, **c**). (**d**) Higher-magnification images of the same dendritic segments indicate a possible frequency of regular spacing along the lateral insertion of dendritic spines (dashes). (**c**, **d**) Monte Carlo envelope tests of these examples. Graphs represent the allowed random band (shaded), the theoretic (theo) distribution function [$G_{CSR}(r)$, red dotted line], and the estimated [$\hat{G}(r)$] obtained from the patterns analyzed (obs, black line) using the proposed edge correction. Because examples did not surpass the shaded envelope (high and low, hi and lo), the null hypothesis of complete spatial randomness was not rejected." (Legend and figure reprinted from Morales et al. (2014) under CC BY license and Copyright Morales, Benavides-Piccione, Dar, Fernaud, Rodríguez, Anton-Sanchez, Bielza, Larrañaga, DeFelipe, Yuste, doi: 10.1523/JNEUROSCI.1085-14.2014)

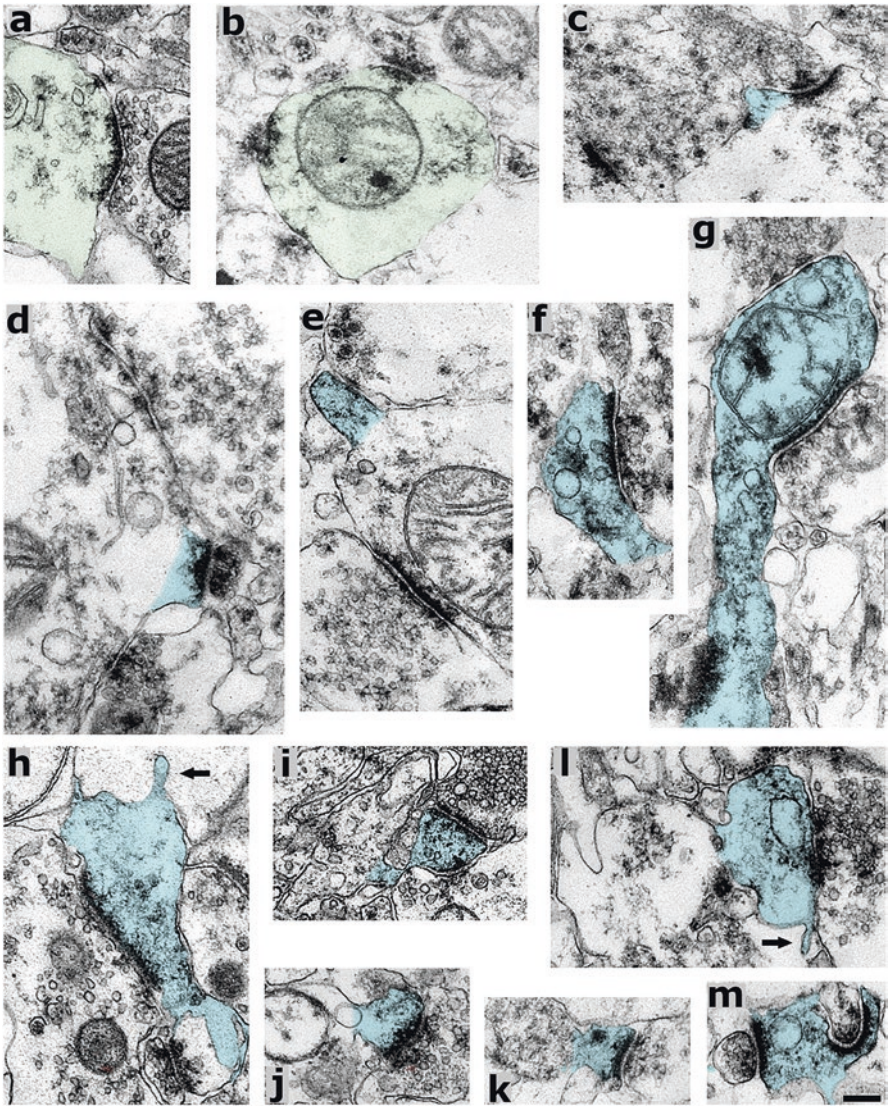

Fig. 9.23 Ultrastructure of dendrites (slightly highlighted in green), spines (blue), and synapses in the human medial amygdaloid nucleus. (**a**) Isolated or (**b**) multiple, adjacent axon terminals making asymmetric synapses upon dendritic shafts were found in the neuropil. Dendritic spines were classified as (**c**, **d**) stubby, (**e**) wide, (**f**) thin with small or (**g**) long necks, (**h**) with a transitional aspect, (**i**–**k**) mushroom shape with small to (**l**) big head and macular postsynaptic densities. A spine with a transitional aspect between mushroom and ramified shapes is shown in (**m**). Spinules are indicated by an arrow in (**h**) and (**l**). Synapses showed asymmetric (e.g., in (**c**, **d**, **f**, **j**, **k**)) or symmetric contacts (in **e** and **i**). Note that the multisynaptic spine receives two asymmetric contacts ((**g**), one at the spine head and another at the neck) and a symmetric contact (at the top of the spine head). Synapses were found at the spine base (**c**), neck (**g**), and head (**i**). Images are from adult individuals. Scale bar = 0.2 μm. (Legend adapted and figures reprinted from Dall'Oglio et al. (2013) under CCC RightsLink® license #5385630478535, and Dall'Oglio et al. (2015) under CCC RightsLink® license #5385561144316, both originally published by John Wiley & Sons, Inc)

Fig. 9.23e). Thin spines ranged in size from small (Fig. 9.23f) to long-necked ones (Fig. 9.23g). This latter can be multisynaptic and show both asymmetric and symmetric contacts at opposite sites on the spine head, and an asymmetric contact at the spine neck (Fig. 9.23g). An example of transitional shaped spine, with morphological features between thin and mushroom types, displayed a protruding spinule that, in this case, showed no evident PSD (Fig. 9.23h). Mushroom spines with variable sizes had small-to-large spine heads (Figs. 9.23i–m and 9.24a), and both symmetric and asymmetric macular synapses (Fig. 9.23i) with asymmetric contacts at the spine head (Fig. 9.23j,k). Mushroom spines also displayed a large head with a perforated PSD (Fig. 9.24a). Spinules were found in multisynaptic mushroom spines (Fig. 9.23l). Spines with other transitional shapes could be observed (with mushroom to ramified features) in some cases (Fig. 9.23m; other atypical/polymorphic examples are shown in Fig. 9.24b, c).

Other interesting ultrastructural findings draw attention to the human MeA: (1) an axonal envelopment around the perimeter of the spine head close to a symmetric synapse (Fig. 9.24d); (2) reciprocal synapses (Fig. 9.24e, top); (3) a multisynaptic spine protruding from an axon showing an unusual spinule-like double-membrane evagination (Fig. 9.24e, bottom and right); (4) a serial axo-axo-dendritic synapse (Fig. 9.24f, bottom); (5) an "*en passant*" axospinous synapse (Fig. 9.24f, top); and (6) the close apposition of cellular membranes suggestive of a "gap-like" junction (Fig. 9.24g and insert; Dall'Oglio et al. 2015). These axonal features in the human MeA neuropil (Fig. 9.8c–e) indicate that connections can be made directly on a specific end-target element or evoke more diffuse synaptic relationships with various cells at the same time. For this latter purpose, the human MeA neuropil shows coarse and finely beaded axons, reinforcing the occurrence of *en passage* synapses, as well as axonal collateral branches forming terminal boutons ranging from simple short appendages to multiple bulbous forms (Dall'Oglio et al. 2013). Bulbous endings can form a glomerular-like synaptic organization, that is, a bulbous axonal vesicle-filled ending making various asymmetric contacts with multiple dendrites at the same time (see Fig. 9J in Dall'Oglio et al. 2013). Taking into account the occurrence of reciprocal (axo–axonal connection) and serial (axo–axo–dendritic connection) synapses, it is very likely that input pathways can generate divergent processing of information in the human MeA. It is hypothesized that such an arrangement would rapidly activate various MeA neurons in parallel and promote a widespread response to the emotionally valenced stimulus and a prompt behavioral display (Dall'Oglio et al. 2015). How this integrated synaptic organization can vary between individuals and according to personal experience is currently difficult to determine and prove, but encourages interesting hypotheses on circuitry functioning.

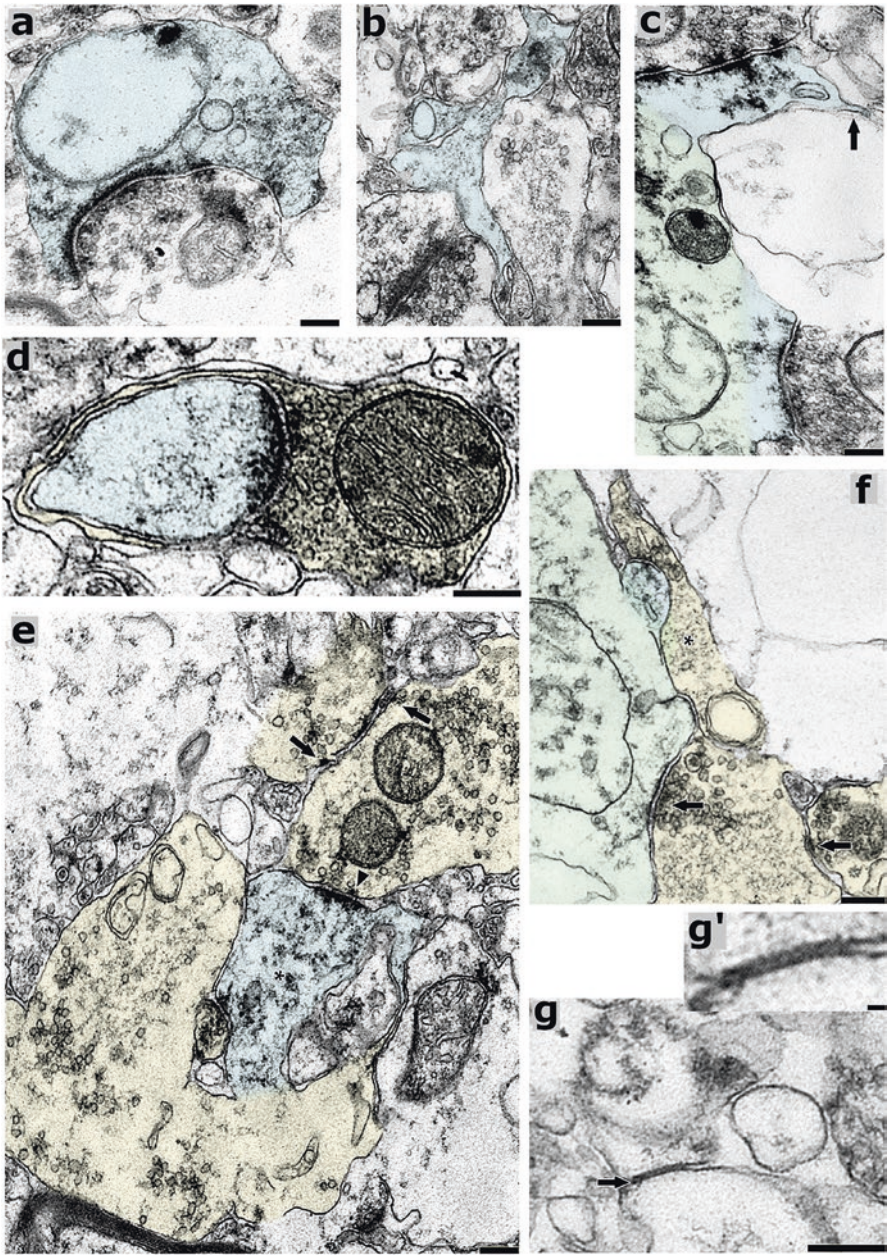

Fig. 9.24 Ultrastructural organization of dendrites (slightly highlighted in green), spines (blue), axons (yellow), and synapses in the human medial amygdaloid nucleus. Some examples of spines synaptic and shape heterogeneity are presented in (**a**–**c**). (**a**) Mushroom spine with a typical large head and a perforated postsynaptic density contacting an axonal bouton with vesicles. (**b**) Atypical spines with ramification and protrusions or (**c**) with an elongated and wide shape and a spinule (arrow). Spines can form complex synaptic arrangements, such as (**d**) an axodendritic asymmetric

9.6 Some Examples of Altered Dendritic Spines in Human Neuropathological Conditions

Various morphological findings on dendritic spines have been obtained from human brain tissue with no evident neuropathological damage or noticeable neurological and psychiatric disorders. The study of spines in normal conditions might serve as the "baseline" for further comparisons with pathological ones. Again, this can be a complex task. First, it is highly expected that some degree of variability in spine number and types can normally occur within the same neuronal subpopulation and brain area. The study of human spines usually involves uncontrollable variables that may influence results (see a parallel discussion in Falougy et al. 2019), which imposes difficulties to determine a suitable sample size considering intra-individual and interindividual variability (see also Forrest et al. 2018). Second, altered dendritic spines can occur in different pathological conditions and since early neurodevelopmental periods to puberty and old age. At the same time, mental health disorders can show different and graded signs and symptoms. The study of dendritic spines and brain connectivity has also to consider differences in men and women as a biological variable in neuropsychiatric research and related to clinical evidence (Joel and McCarthy 2017; Rubinow and Schmidt 2019; Sheppard et al. 2019; Arnold 2020; Hidalgo-Lopez et al. 2021).

Despite these inherent difficulties, neurological and psychiatric disorders have been associated with cross-scale disruptions in the synaptic organization, spine structure, functioning of individual cell types, and wiring of microcircuits in the human brain (Hunt et al. 2022 and references therein). Dendritic spine abnormalities have been classified as "pathologies of spine distribution" and "pathologies of ultrastructure" (Fiala et al. 2002). The former affects the number, morphology, and loci of spine origin on the neuron. In other words, there can be increases and decreases in spine density, alterations in spine size and distortion of spine shape, dendritic swellings with concomitant loss of spines, and ectopic spines (Fiala et al. 2002). The latter involves distortion of the ultrastructure and the subcellular organelles within dendritic spines, including electron-dense spines, altered endoplasmic reticulum, hypertrophied spine apparatus, multivesicular bodies and cytoskeleton, with higher spine volume in giant spines, and formation of aberrant synapse-like connections with axonless spines and axon-free PSDs (Fiala et al. 2002). The

Fig. 9.24 (continued) contact with an axon that envelopes the spine head, (**e**) axo-axonal reciprocal synapse (arrows close to synaptic vesicles), and an axospinous asymmetric contact (arrowhead) in an axonal spine (asterisk) with an atypical "spinule-like" double-membrane evagination (right), and (**f**) serial axo-axo-dendritic synapse (arrows) and an *en passant* axospinous synapse (asterisk). In (**g**), the close appositions of membranes resemble a gap-like junction (arrow; at high magnification in the insert **g′**). Images are from adult individuals. Scale bar = 0.2 μm, except for the inserts where scale bar = 20 nm. (Legend adapted and figure reprinted from Dall'Oglio et al. (2015) under CCC RightsLink® license #5385561144316, originally published by John Wiley & Sons, Inc)

study of the synaptic signaling cascades and the integrated molecular pathways that lead to irregular dendrites and altered spine structure–function coupling is key to unraveling the different groups of neuropsychiatric disorder-associated risk factors and patients' clinical characteristics (Penzes et al. 2011; Chassefeyre et al. 2015; Hrvoj-Mihic et al. 2017; Forrest et al. 2018; Kommaddi et al. 2018; Runge et al. 2020; Heinze et al. 2022).

Genetic and environmental risk factors can alter putative trajectories of dendritic spines morphogenesis and pruning during typical development or in neuropsychiatric disorders (Forrest et al. 2018). Converging on a subset of networks and pathways, both hypoconnected and hyperconnected cells disrupt short- and long-range networks in the brain, affecting different psychological domains and how symptoms are displayed (Forrest et al. 2018). Dysregulation of dendritic and spine structure and dynamics occur in various neurodevelopmental, neuropsychiatric, and neurodegenerative disorders. The list of spinopathies includes the affected brain following malnutrition, alcohol or toxin exposure, infection, maternal phenylketonuria, autism spectrum disorder (ASD), Fragile X syndrome, Rett syndrome, Williams syndrome, Creutzfeldt–Jakob disease, frontal dementia, Alzheimer's disease (AD), Pick's disease, Parkinson's disease, Huntington's disease, schizophrenia, bipolar disorder, epilepsy, hypoxic or ischemic insults, traumatic lesions, and brain tumors.[22]

It is not completely clear whether altered spines are the cause, consequence, compensatory response, or a combination of these possibilities in each studied disorder and spectrum of clinical presentation (Fiala et al. 2002; Penzes et al. 2011). Although it is currently unsettled whether morphological changes in spines are associated with the time course of specific symptoms, "spine alterations may be relevant no matter where in the pathological cascade of a disease they occur" (Penzes et al. 2011). Indeed, pioneer works with Golgi-impregnated neurons reported remarkable morphological abnormalities of dendritic spines in cases of children clinically diagnosed with intellectual disability compared to children with normal cortical development and behavior. Human neocortical pyramidal neurons display spines whose number normally increases from the fetal to infancy periods, as mentioned previously (Fig. 9.25a). Genetic disorders that cause intellectual disability (e.g., Patau syndrome and Down syndrome) are associated with abnormal distribution, number, and shapes of dendritic spines in neocortical neurons along the postnatal development (Marín-Padilla 1972, Fig. 9.25a). Neurons have long fine spines with multiple varicosities on pedicles, entangled spines, and expanded terminal heads (Purpura 1974, Fig. 9.25b).

The abnormal morphology of dendritic spines is associated with neuropsychiatric disorders such as ASD and schizophrenia. Besides other affected brain areas (e.g., the frontal, parietal, and temporal lobes), there is a high dendritic spine density with more immature shapes in the human lateral amygdaloid nucleus in ASD

[22] For relevant data, see Baloyannis et al. (2001), Fiala et al. (2002), Penzes et al. (2011), Jiang et al. (2013), Overk and Masliah (2014), Maiti et al. (2015), Herms and Dorostkar (2016), Hrvoj-Mihic et al. 2017, Forrest et al. (2018), Chidambaram et al. (2019), Runge et al. (2020), Bączyńska et al. (2021), and Parajuli and Koike (2021), for example.

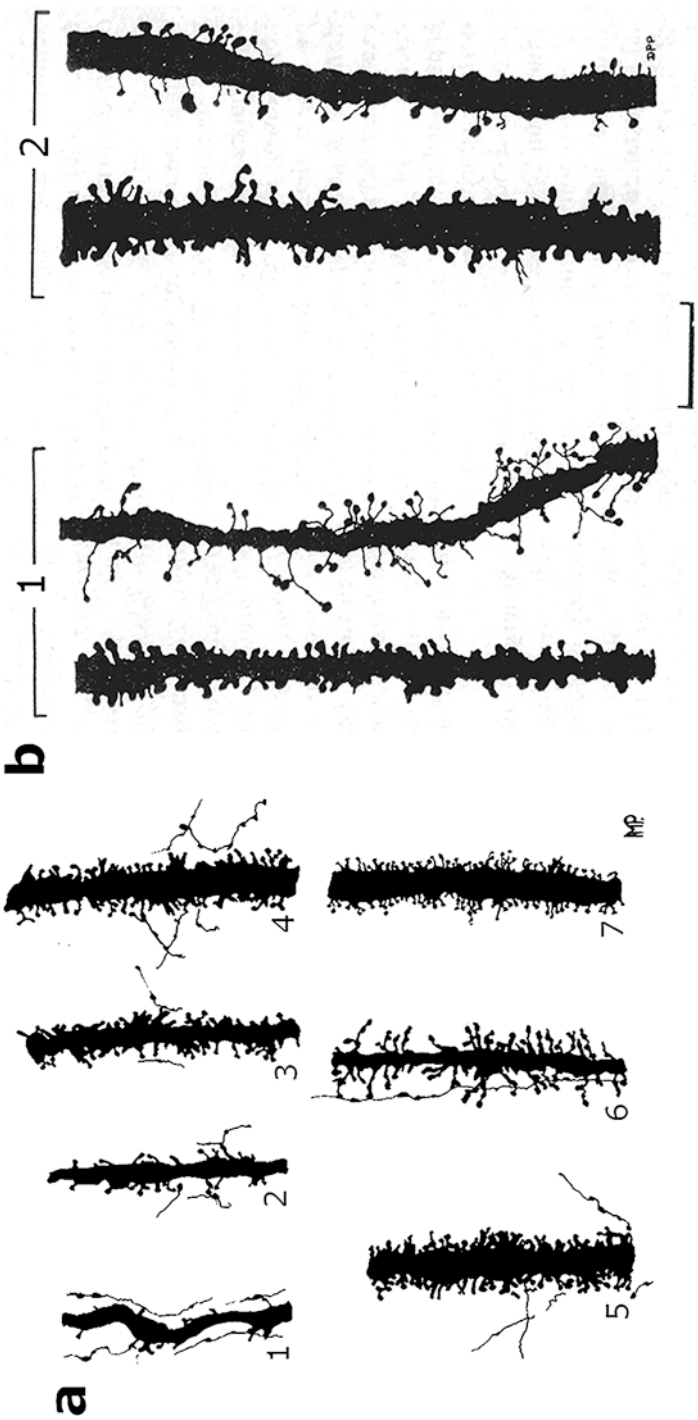

Fig. 9.25 (*caption on p. 459*)

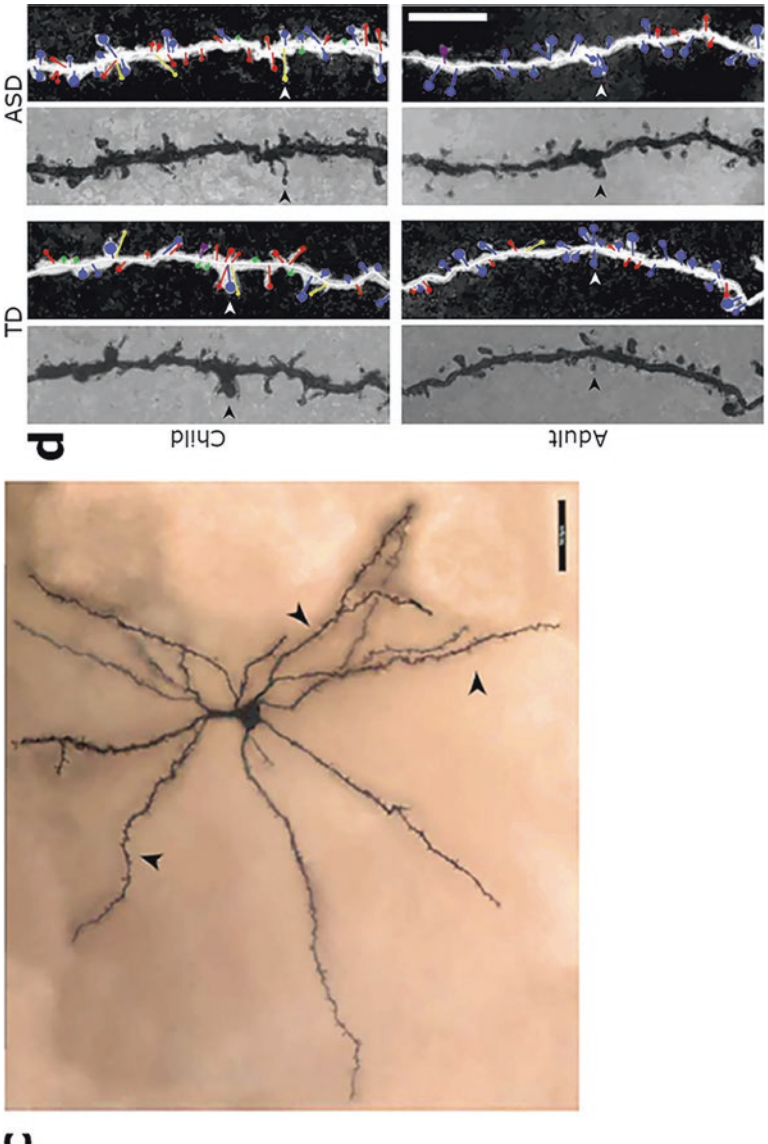

Fig. 9.25 *(caption on p. 459)*

individuals than in control individuals (Weir et al. 2018, Fig. 9.25c). This finding might be associated with some ASD symptoms, such as disruption in information processing and deficits in social interactions because the integrity of the amygdaloid nuclei and their connections are relevant for emotional processing, memory and cognition, anxiety and stress regulation, and proper social behavior display (Rasia-Filho et al. 2000; Šimić et al. 2021). Moreover, Golgi-impregnated pyramidal neurons from the dorsolateral prefrontal cortex display a reduced density of dendritic spines in subjects diagnosed with schizophrenia (under treatment with antipsychotic agents) compared to control data (Glantz and Lewis 2000). Reduced spine density was also found in the parietal cortex in these cases (Garey et al. 1998). Spines in higher-order cortical areas process synaptic information from multiple circuitries for executive functions and proper social behavior display, some of which are specific to humans. Then, deficits in synaptic transmission in these areas might account for some of the clinical findings of these patients (see more data in Lewis and González-Burgos 2008; Jaaro-Peled et al. 2010; Penzes et al. 2011; Orellana and Slachevsky 2013).

Fig. 9.25 (**a**) Camera lucida drawings of Golgi-impregnated spiny apical dendrites of layer V pyramidal neurons (crossing the territory of layer III) in the human motor cerebral cortex. Data were obtained along normal development and from genetic disorders. The apical dendritic segments are from (1) a 5-month fetus; (2) a 7-month fetus; (3) a newborn; (4) a 2-month-old infant; (5) an 8-month-old infant; (6) a newborn girl with 13–15 trisomy (Patau syndrome); and (7) an 18-month-old girl with 21 trisomy (Down syndrome). Images illustrate the morphological characteristics of the human dendritic spines during prenatal and early postnatal cortical development (1–5). The number of spines normally increases with age. The spines from two infants with proven chromosomal trisomies and intellectual disability have abnormal distribution, number, and shapes (6, 7). (Legend adapted and figure reprinted from Marín-Padilla (1972) under CCC RightsLink® license #5387100803473, originally published by Elsevier). (**b**) Camera lucida drawing of Golgi-impregnated dendritic segments of medium-sized pyramidal neurons of the human motor cortex in normal conditions (infant and child) or cases with intellectual disability. (1, left) Normal aspect for the dendritic spines of a 6-month-old infant. Three basic types of spines were identified: thin, stubby, and mushroom-like spines. (1, right) Dendritic spines from a 10-month-old infant with intellectual disability displaying abnormally long spines and some entangled spines with prominent terminal heads. Multiple varicosities on the pedicles of these long, thin spines were occasionally found, but mushroom-like and stubby spines were rarely observed in this case. (2, left) Apical dendrite of a normal 7-year-old child. (2, right) Apical dendritic segment from a 12-year-old child with severe intellectual disability. The paucity of mushroom-like and stubby spines and the presence of thin spines with abnormally expanded terminal heads are characteristics of this case. Scale bar = 10 μm. (Legend adapted and figure reprinted from Purpura (1974) under CCC RightsLink® license #5387120853098, originally published by Science, The American Association for the Advancement of Science). (**c**) Two-dimensional photomicrograph of a Golgi-impregnated principal neuron from the human lateral amygdaloid (La) nucleus. Arrows indicate second-order dendrites where dendritic spines were studied in control (typical development, TD) and autism spectrum disorder (ASD) cases from youth to adulthood. (**d**) Representative high-magnification images of second-order dendrites and spines (arrowheads) of La neurons. Each Golgi-impregnated figure is accompanied by a representative trace image. Spine density in child ASD cases was higher compared to age-matched TD cases and adult ASD cases. Young ASD cases also display spines that tend to be more immature than TD cases. Blue: mushroom spine; red: thin spine; yellow: filopodial spine; green: stubby spine; purple: branched spine. Scale bar = 50 μm (in **c**) and 10 μm (in **d**). (Legend adapted and figures reprinted from Weir et al. (2018) under CCC RightsLink® license #5387140851871, originally published by John Wiley & Sons, Inc)

9.6.1 Additional Data on Alzheimer's Disease

Different experimental and imaging approaches for the study of the net loss of dendritic spines in AD opened a new frontier for research. For example, human hippocampal CA1 pyramidal neurons with and without tau pathology were imaged using intracellularly Lucifer Yellow fluorescent dye and confocal microscopy (Mijalkov et al. 2021; Fig. 9.26a). The number of dendritic spines is reduced in hippocampal pyramidal neurons and dentate granule cells in AD cases (Fiala et al. 2002; Penzes et al. 2011). In this case, the presence of tau pathology determines the loss of dendritic spines in clusters (not at random) in neocortical pyramidal neurons, letting the remaining spines in smaller, more tightly packed, and isolated groups along dendritic segments (Mijalkov et al. 2021; Fig. 9.26a). Dendrites passing through or near fibrillar β-amyloid deposition show a progressive reduction in dendritic number, shaft diameter, and length also related to local axonal abnormalities and permanent disruption of neuronal connections (Tsai et al. 2004). At least part of the cognitive dysfunction in AD may be related to this degree of disruption of spatial location of dendritic spines, their function and connectivity, affecting the modulated synaptic organization and plasticity from subcortical to allocortical- and neocortical-associated regions (Heimer et al. 2008; Overk and Masliah 2014; Rasia-Filho et al. 2021).

Fig. 9.26 (**a**) Human hippocampal CA1 pyramidal neurons with and without tau pathology in Alzheimer's disease (AD). Confocal microscopy images of merged images (*a'*, *d'*) following intracellularly injected Lucifer Yellow fluorescent dye (green, *b'*, *e'*) and immunostaining with phospho-tau AT8 (red, *c'*, *f'*). Neurons (*a'-f'*) and their basal dendrites and spines (*g'-m'*) are shown in different tau pathology conditions. Dendrites from cell body neurons immunostained by either phospho-tauAT8 or phospho-tauPHF-1 were classified as "SomaTau+" dendrites, whereas those not immunostained by either of these antibodies were labeled as "SomaTau-" ones. (*a'-c'*, *g'*, *i'*) Neurons and dendrites from a cell body free of phospho-tau AT8 and (*d'-f'*, *h'-j'*) with phospho-tau AT8 in an intermediate stage of neurofibrillary pathology. Note the different number of dendritic spines between dendrites SomaTau- and SomaTau+ (lower in this latter) in the zoomed-in views of dendrites and spines (from *g'* to *j'*). The high-resolution dendritic segment in *k'* demonstrates the spines along the white line shown in *j'*. Red points indicate spines on the dendritic shaft (*l'* and *m'*), their three-dimensional spatial distribution, and insertion points (*m'*). Dendritic spines were lost in clusters. Scale bar (shown in *m'*) = 12 μm (*a'-f'*), 5 μm (*g'-j'*), and 3 μm (*k'-m'*). (Legend adapted and figure reprinted from Mijalkov et al. (2021), https://doi.org/10.1038/s41598-021-91726-x, under CC BY 4.0 copyright license). (**b**) Focused ion beam/scanning electron microscopy images and postsynaptic target identification in the *stratum pyramidale* and *stratum radiatum* in the hippocampal CA1 field of control and AD cases. (*a'*) Dendritic shaft (blue) with a protruding dendritic spine (purple). Axospinous asymmetric synapse (Asym, white arrowhead) established on the head of the spine. (*b'-e'*) Axospinous asymmetric synapse followed through the stack of images. (**c**, **d**) The percentage of axospinous and axodendritic asymmetric synapses (**c**) and symmetric synapses (**d**) in the *stratum pyramidale* (str pyr) and *stratum radiatum* (str rad) of CA1 in both control and AD cases. Lower values were found in AD cases. Scale bar in E = 500 nm (*a'*) and 450 nm (*b'-e'*). (Legend adapted and figure reprinted from Montero-Crespo et al. (2021) under CCC RightsLink® license #5387231262727, originally published by Oxford University Press)

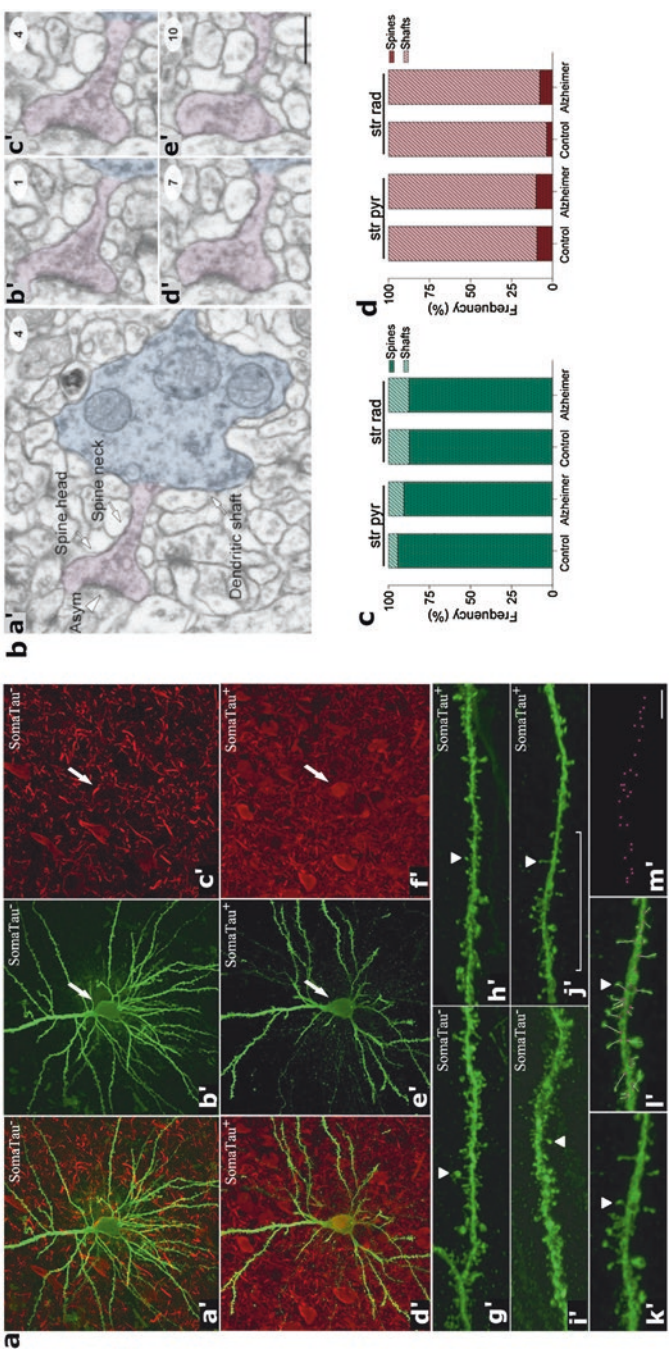

Fig. 9.26 *(caption on p. 460)*

In the same regard, recent 3D analysis of focused ion beam/scanning electron microscopy (FIB/SEM) images identified changes in the synaptic organization in the *stratum pyramidale* and *radiatum* in the hippocampal CA1 field of subjects diagnosed with AD (Fig. 9.26b). Axonal synapses on spine heads showed an asymmetric aspect that was the most abundant type, multisynaptic spines were observed in small numbers, and axospinous symmetric synapses were scarce in both strata (Montero-Crespo et al. 2021). Compared to controls, AD cases have a lower proportion of axospinous asymmetric synapses (with a diminished proportion of perforated PSD) and a higher frequency of axodendritic asymmetric synapses in the *stratum pyramidale* (Fig. 9.26c). In the *stratum radiatum*, a lower proportion of axodendritic symmetric synapses is found in AD cases compared to controls (Fig. 9.26d). In both strata, a lower proportion of large asymmetric synapses (mainly axospinous and macular synapses) exist in AD cases (Montero-Crespo et al. 2021).

The human medial entorhinal cortex (EC) is another critical area related to cognitive deficits in the course of AD (Domínguez-Álvaro et al. 2021a, b). The 3D analysis of FIB/SEM images served for the description of the synapses in the neuropil of medial EC in layers II and III from human brain autopsies (Domínguez-Álvaro et al. 2021a). The proportion of asymmetric and symmetric synapses on the dendritic shaft, on the spine head or neck, and the number and type of single or multiple axospinous contacts were determined for both layers in normal subjects (Fig. 9.27). In both layers, most synapses were of the asymmetric type presenting a macular morphology. Approximately half of the asymmetric contacts were made on dendritic shafts and half were on spine heads (usually one single axonal contact per spine). The majority of symmetric contacts were found on dendritic shafts and the remaining on spine heads (Domínguez-Álvaro et al. 2021a). In AD patients, there was a significantly lower synaptic density in both layers, asymmetric synapses were larger and more complex ("horseshoe-shaped") in layer II, and asymmetric synapses were smaller and simple (fragmented and macular were more frequent, whereas perforated was less frequent) in layer III compared to control individuals (Domínguez-Álvaro et al. 2021b).

Fig. 9.27 (*Left and Center*, **a**–**d**) Synaptic morphology analysis and identification of postsynaptic target distribution in the neuropil of layers II (**a**, **b**) and III (**c**, **d**) of the human medial entorhinal cortex (EC) under focused ion beam/scanning electron microscopy. (**a**) Distribution of asymmetric synapses (AS, green, considered excitatory) and symmetric synapses (SS, red, considered inhibitory) contacting postsynaptic targets (spine head and neck or dendritic shaft) in EC layer II. (**b**) Schematic representation of the proportions of AS and SS on different postsynaptic targets in EC layer II. (**c**) Distribution of AS and SS contacting different postsynaptic targets in EC layer III. (**d**) Schematic representation of the proportions of AS and SS on different postsynaptic targets in EC layer III. In (**b**) and (**d**), note - from left to right - the most frequent type (AS on dendritic shafts) to the least frequent type (SS on spine necks) of contact. (*Right*) Schematic representation of single excitatory synapses and multiple excitatory ones with or without inhibitory synapses upon the head of dendritic spines in EC layers II and III. Percentages of each synaptic type are indicated. Note that one single excitatory contact on the spine head is the most frequent type. Synapses on the necks and other combinations were rarely observed (less than 1%) and were not included. (Legend and figure slightly adapted and reprinted from Domínguez-Álvaro et al. (2021a) under CCC RightsLink® license #5386740499269, originally published by Oxford University Press)

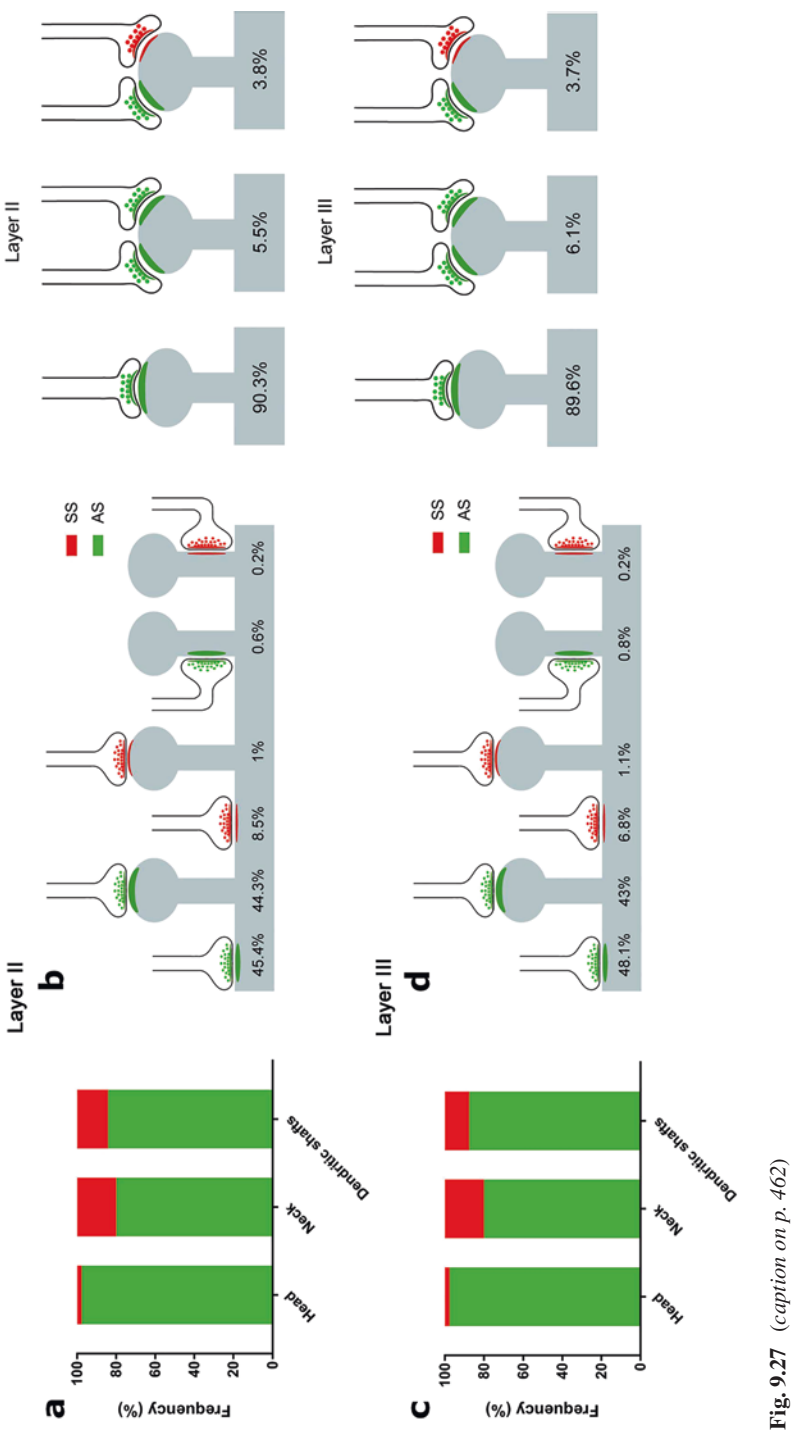

Fig. 9.27 *(caption on p. 462)*

A reduction in the number of apical dendritic spines on cortical pyramidal neurons was also reported in AD (three patients), Parkinson's disease and dementia (one patient), Creutzfeldt–Jakob disease (four patients), Pick's disease (one patient), and dementia paralytica (one patient; Catalá et al. 1988). In conjunction, these data indicate that altered excitatory synapses on dendritic spines are likely associated with impaired synaptic and information processing in areas and neurons vulnerable to tau pathology, β-amyloid deposition, AD progression, and other dementia cases. Structural, metabolic, perfusional, and functional pathological changes can be associated with cognitive decline in AD patients, which can initiate many years before the unequivocal clinical diagnosis of a symptomatic disorder.

On the other hand, cognitive resilience to AD pathology can occur in older individuals with abnormal brain levels of β-amyloid plaques and neurofibrillary tangles (Boros et al. 2017). Golgi-impregnated dendritic spines in layers II/III pyramidal neurons from the dorsolateral prefrontal cortex showed interesting results in these cases compared to age-matched pathology-free controls and AD cases. Spine density and, specifically, thin and mushroom spines were reduced in AD cases. Mean spine head diameter also showed lower values in AD. On the other hand, cognitively resilient persons showed the same spine density as normal controls, few stubby spines (but a higher length for this type of spine), and reduced thin spine head diameter compared to controls and AD cases (Boros et al. 2017). These findings suggest that maintenance of certain dendritic spine types, remodeling of their shape, and modulation of synaptic activity would protect older individuals with AD pathology from developing dementia (Boros et al. 2017; see also Walker and Herskowitz 2021). The study of vulnerable neuronal subtypes, the participation of glia and other cells in the local inflammatory and oxidative stress, and the altered neural and circuitry excitability are fundamental steps to elucidate the pathogenesis of AD. They will improve our knowledge about neuroprotection (Lourenço et al. 2019) or timely diagnosis and, hopefully, the possibility to halt progressive neurodegenerative processes and impaired functions in affected brain areas and circuitries.

9.7 Final Remarks and Perspectives

As evidenced by the existence of heterogeneous "aspiny" neurons or cells with very sparse spines along the CNS, morphological data indicate that spines may not be crucial for every information processing in all human neural circuits. Examples are found from the spinal cord to various brainstem, diencephalic, and cortical areas. Axons terminating directly upon smooth dendritic shafts might promote "direct" and less modulated synaptic responses than those made upon spines. In both aspiny and spiny cells, the neuronal input/output ratio depends on the presynaptic elements' activity, the synaptic transmission, and all the postsynaptic responses, including the dendritic tree's biophysical and biochemical attributes. Non-spiny neurons might have more variability in the EPSPs occurring at different dendritic locations and, within certain ranges, with no "low-pass filters" for synaptic

transmission represented by spines (adapted from Tsay and Yuste 2004; Gulledge et al. 2012). Circuits may have cells devoid of spines or with sparse spines aiming for a cellular activity pattern that would show varied amplitudes for the dendritic EPSPs (related to the resting potential, input resistance, and membrane time constant) and, accordingly, input/output ratios for fast firing patterns depending on timely synaptic demands.

On the other hand, dendritic spines are evident in neurons coexisting with other aspiny cells along the CNS and, notably, in "higher-order" brain areas. For example, most neurons of evolved cortical areas that integrate unimodal to multimodal information are spiny ones. Although spines are not always needed to connect pre- and postsynaptic sides, when doing so they provide many more modulatory and plastic possibilities for signal integration upon dendrites. Spines enhance wiring possibilities, maximize connectivity with several different axons, and form networks with increased flexibility and high computational power. Spines can modulate the strength of synaptic inputs along different dendritic distances and branching orders. Spines also expand the complexity of synaptic processing by adding varied molecular pathways for activity-dependent integration and learning along dendritic segments. Various projecting neurons in the CNS are spiny, which implies that they compute numerous different and dynamic inputs, modulate, and integrate them before sending an output code onward within each respective neural circuit. The heterogeneity of spine number, distribution, shapes and sizes indicate a myriad of malleable computational possibilities for these neurons and networks. Some complementary possibilities are commented on in this final analysis.

Spiny pyramidal neurons have significant phylogenetic, ontogenetic, and functional development (Rasia-Filho et al. 2021 and references therein; see also Chaps. 4, 7, and 8 in this book). The excitability of cortical pyramidal cells is determined by thousands of spines along hundreds of micrometers of main dendritic shafts and collaterals with spatiotemporal integrative synaptic properties. From approximately 100 trillion spines in the human cortex (Kasai et al. 2021), nearly 99.5% of all spines lie in pyramidal neurons (Kubota et al. 2016) organizing the ongoing synaptic transmission from multiple neurochemical circuits (Palomero-Gallagher and Zilles 2019). Aspiny and spiny interneurons compose local microcircuits (Kubota et al. 2016; Foggetti et al. 2019). Ten or more cortical GABAergic non-pyramidal cell subtypes with a unique form of axonal arborization and innervation pattern control the excitation of these pyramidal neurons (Kubota et al. 2016). Pyramidal neurons and circuits have notable human-specific features within the expanded cortical layers II/III. Spines reflect past and ongoing synaptic demands for each neuronal type, area, and network. Based on this scenario, it is plausible to suppose that we will still discover more cellular and connectional particularities in our species when looking for areas with a higher development in primates and for our distinguished behaviors.

Here, one insight deserves additional consideration, that is, when mentioning that "dendritic spines are postsynaptic units" we are also indicating the existence of three "worlds" of functional specialization and evolution working together

(i.e., *dendrites* plus *spines* plus *synapses*). Each component has its complexity and active role in modulating information that, jointly, provide much more functional possibilities to information processing (Sjöström et al. 2008; Sala and Segal 2014; Nakahata and Yasuda 2018; Rollenhagen et al. 2020; Schmidt and Polleux 2022). The timely and spatially integrated actions by these elements generate multiple properties for the beginning of emergent features in assembled cells within neural networks. They are also associated with neural organization occurring on a full range of scales, from synaptic structure and individual proteins to changes in long-distance connectivity and gray and white matter volumes (Mancuso et al. 2014).

Indeed, spines have the capacity to modulate the magnitude of the EPSPs and associate them with the geometry and functional properties of the dendritic arbor. It is then important to determine the actual impact of spines on neuronal activity. Spines can integrate the inputs received and transform synaptic inputs into a variety of linear and nonlinear voltage signals in the parent dendrite (Spruston 2008). Depending on voltage dynamics in spines (Cornejo et al. 2022) and the specific form of dendritic integration (i.e., from summed EPSPs to brief or prolonged dendritic spikes), dendrites can show a single AP, trains and bursts of multiple APs (Losonczy and Magee 2006). Even a partial fusion of active spines or changes in spine branch positions would increase synaptic signal transfer (Rusakov et al. 1996). For example, glutamate evokes local dendritic spikes in rat CA1 pyramidal neurons. Somatic voltage responses show a nonlinear increase when such stimulations are performed in rapid succession at multiple spots either clustered or distributed along the dendritic segment, although the dendritic spike threshold is lower for the distributed input than for the clustered one (Losonczy and Magee 2006; Spruston 2008). These synchronous and sized input patterns would be represented by a tightly clustered stimulation of ~20 inputs within ~6 ms (i.e., 20 synapses would represent ~30% of all synapses within 20 μm in this specific dendritic segment), whereas distributed stimuli would be represented by the activation of spines randomly covering approximately 67% of a single oblique dendrite (along ~60 μm; Losonczy and Magee 2006). By modeling human temporal layer II–III pyramidal neurons, a somatic AP would be generated (with 50% probability) by 134 ± 28 simultaneously activated synapses with large AMPA and NMDA conductances per synaptic contact, with EPSPs at the spine head of 12.7 ± 4.6 mV, and at spine base of 9.7 ± 5.0 mV (Eyal et al. 2018). Based on the extension of the pyramidal neuron dendritic arbor (in μm and with different domains) and the number and location of pleomorphic spines, the activation of a relatively a few number of dendritic spines provides neurons with many different possibilities to elaborate a flexible input–output code within neural circuits.

Let us consider again the likely integrative action made by a human long and densely spined CA1 hippocampal neuron (as shown in Fig. 9.15) in the context of our current knowledge about this area and spines' features. The CA1 area has a relevant role in encoding memories along with integrated and widespread circuits that endow us with a clear notion of who we are, where we stay, and the time we live in. Dendrites are capable of compartmentalization combined with amplification, inhibition, and neuromodulation of inputs for routing and multiplexing streams of

information (Payeur et al. 2019). Spines are multifunctional integrative units (Shepherd 1996) with a turnover rate (formation and shrinkage), varied number, and a *continuum* of shapes and sizes that compute and modulate the network state with multiple spatiotemporal axonal inputs reaching every single cell. Pre- and postsynaptic elements may show associated structure and function in terms of connective strength (Leopold et al. 2019), with the former adjusting the speed of learning and postsynaptic firing rates, whereas postsynaptic plasticity can also amplify the response range (Mizusaki et al. 2018). Contextual information processing and different types of local computations and organizational gradients (Shafiei et al. 2020) as well as synaptic-induced voltage transients and molecular cascades beginning in the intraspine microenvironment can spread to neighbor spines and within the parent dendrite and onward (Harvey et al. 2008; Sala and Segal 2014; Cornejo et al. 2022). Together with glial cells and extracellular matrix, it is formed a system with a very large range of possible activities, from the nanoscale to major networks functioning, using both stable and plastic characteristics. The specialization of our neural cells and the expanded connectivity of the human neuropil can involve unique elements (Cajal 1909–1911; DeFelipe 2011; Schmidt and Polleux 2022). Approximately 10% of the proteins encoded in the human genome can be found composing synapses, their diversity and individual function (Grant and Fransén 2020) in complex PSD compositions (Cohen 2013). Over 500 different types of molecules modulate the structure and function of dendritic spines (Ammassari-Teule et al. 2021; see also Calabrese et al. 2006 and Helm et al. 2021). The *dendrites* plus *spines* plus *synapses* and their rich network features provide emergent functions expanding our capacity for learning and adaptive responses. This is part of the complexity elaborated by one single neuron in a conjunct of millions of other neural cells composing one unique person.

There are still many unexplored human brain areas, and more data are needed for the characterization of human neurons in an integrated functional context. New experimental frontiers offer exciting perspectives for the detailed characterization of individual neuronal profiles within areas and networks (González-Burgos et al. 2019; Gouwens et al. 2019). They involve "multi-omics" and multiple molecular signatures associated with computational approaches (Luo et al. 2022), and multineuron patch-clamp recordings and morphology assayed from the same cells in neurosurgically resected human brain tissue (Hodge et al. 2020; Berg et al. 2021; Planert et al. 2021). The number of neuronal types can be impressive. For example, by revealing conserved cell types with divergent features, 24 excitatory and 45 inhibitory transcriptomically distinct neuron types were identified in the middle temporal gyrus in humans (Hodge et al. 2019). Non-neuronal cell types had the most-divergent expression of genes comparing human and mouse temporal cortex (Hodge et al. 2019). Joint analyses of the methylome, transcriptome, chromatin accessibility, and conformation revealed 63 cell finely defined populations in the human frontal cortex, including 19 excitatory neuronal subtypes, 33 inhibitory neuronal subtypes, and 11 non-neuronal cell subtypes (Luo et al. 2022). In addition, human cortical pyramidal neurons in supragranular layers show electrophysiological characteristics that support their subdivision into five different functional

subpopulations (Berg et al. 2021; Planert et al. 2021; see relevant mice data in Gouwens et al. 2019; Fig. 9.28a, b). The characterization of dendritic spines in these specific neuronal subpopulations is highly desirable (as done to describe gonadotropin-releasing hormone cells, Campbell et al. 2005; see also the work of González-Burgos et al. 2019).

Furthermore, neuron morphology is a major source of wiring specificity and nonrandom cortical network topology in addition to genetically defined cellular identity and molecular recognition of cell type and activity (Udvary et al. 2022). However, axodendritic overlap does not predict connectivity. Spines from one dendrite can be completely intermingled with the spines of other dendrites and various axons can be close to a spine, but most juxtapositions of the trajectories of excitatory axons with dendritic spines do not establish synapses in the mouse cerebral cortex (Kasthuri et al. 2015; Udvary et al. 2022). On the other hand, "the greater the cellular diversity, the broader are the distributions of connection probabilities" (Udvary et al. 2022; Fig. 9.28c). This is a finding that can advance with paired recordings from synaptically coupled neurons and by combining electrophysiological properties with 3D structural and molecular profiles to characterize both pre- and postsynaptic neurons at the light and electron microscopic level in local brain microcircuits, including human samples (Qi et al. 2020; see also Kubota et al. 2018 and Leopold et al. 2019).

Complementary approaches are needed toward a unified, consensual neuronal classification based on a high-throughput single-cell transcriptomic-based taxonomy, building a "probabilistic definition" of every cell type along brain regions (Yuste et al. 2020; see also Peng et al. 2021). We will need to critically evaluate intra- and inter-type variability in cellular phenotypes along different ages, brain areas and their synaptic demands (Lodato and Arlotta 2015; Fuentealba-Villarroel et al. 2022) as well as taking into account that transcriptional profiles and cell-specific molecular responses can vary between individuals (Xu et al. 2018). "The existence of cell states, spatial gradients of phenotypes and mixtures of differences and similarities in cross-species comparisons present challenges to a discrete and categorical perspective on defining cell types. Prematurely adopting an inflexible definition of types will obscure the significance of observed phenotypic variability and its biological interpretation…" while might exist a "… core and intermediate cells or the description of a cell type as a continuous trajectory in transcriptomic space" (Yuste et al. 2020). When doing so with advancing techniques, additional perspectives will emerge for relating human-specific genomic features with morphology, connectivity of specific neuronal subpopulations, dendritic spines, and synaptic structure and composition (Kommaddi et al. 2018; Xu et al. 2018; Helm et al. 2021; Fuentealba-Villarroel et al. 2022; Hunt et al. 2022; Schmidt and Polleux 2022; see the modular nanomolecular architecture of synaptic proteins described in mice and rats by Hruska et al. 2018). For example, intraspine nanodomains with biochemical cascades and proteins can remodel the dendritic spine structure. Current approaches can evaluate the polymerization/depolymerization ratio of actin in normal and pathological conditions (Fig. 9.29). Integrating foundational knowledge and clinical findings can open new possibilities to understand the

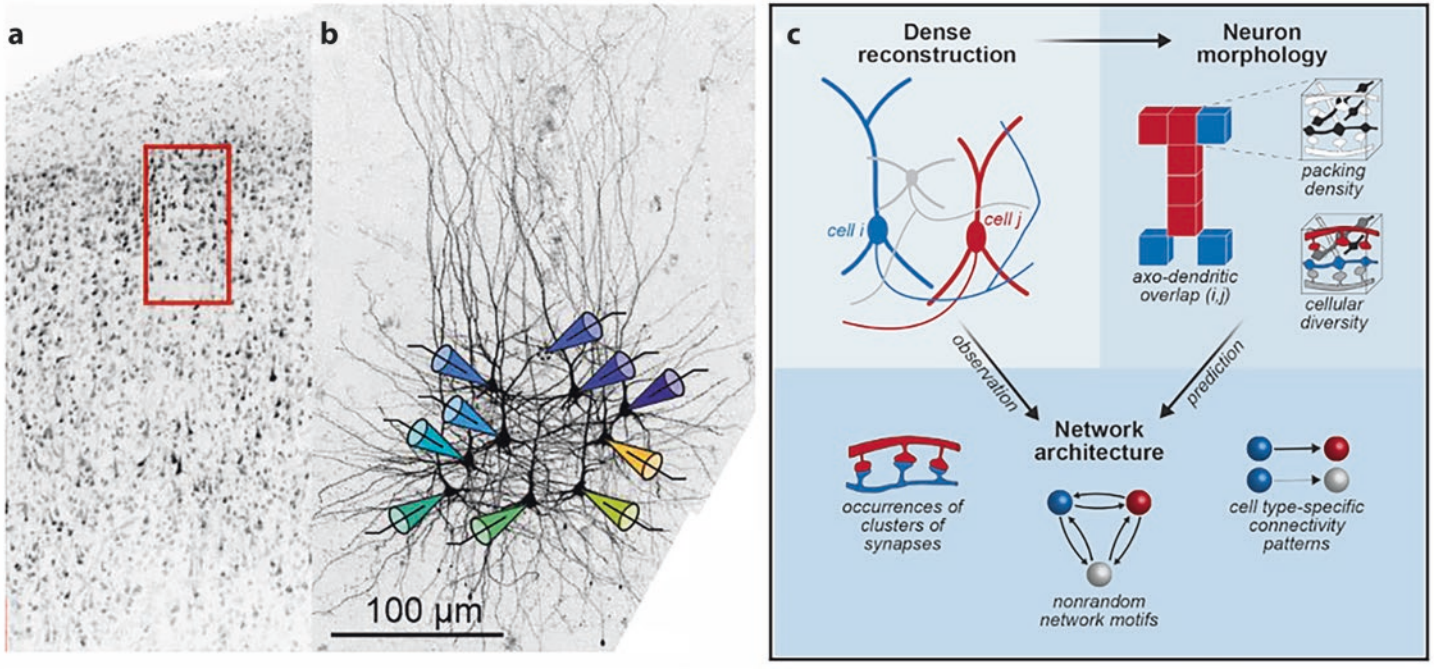

Fig. 9.28 High-throughput whole-cell patch-clamp recordings can be performed in human cortical brain tissue *ex vivo* providing hundreds of pyramidal neurons for electrophysiological and morphological study. (**a**) Nissl staining of human cortical cell layers. Cells from layer II and III cells (indicated by a rectangle) were sampled for further study. (**b**) Colored patch pipettes illustrate the multi-neuron patch-clamp approach. Neighboring pyramidal neurons were electrophysiologically recorded and, afterward, biocytin stained to unravel their morphology. (Legend adapted and Figure reprinted from the original work by Planert et al. (2021) https://doi.org/10.1101/2021.11.08.467668; copyright CC BY 4.0 International license). (**c**) To test the impact of neuron morphology on network connectivity, reconstructed 3D geometry and cytoarchitecture of a brain area of interest were obtained and the morphology and classification of neurons inside a selected volume were determined (in this case, neurons are labeled *i* in blue and *j* in red). Afterward, within brain subvolumes, the axodendritic overlaps were identified. Note the representation of neuron *j* and the axonal projections of neuron *i* contacting it related to the local packing density of presynaptic axons (black), postsynaptic dendrites, and spines (white) as well as the cellular diversity (i.e., the number of neurons from which the presynaptic and postsynaptic elements originate). Predictions and empirical observations are then compared for the existence of clusters of synapses, nonrandom network motifs, and cell-type-specific connectivity patterns. (Figure reprinted from Udvary et al. (2022) under CCC RightsLink® license #5440750664829, originally published by Elsevier)

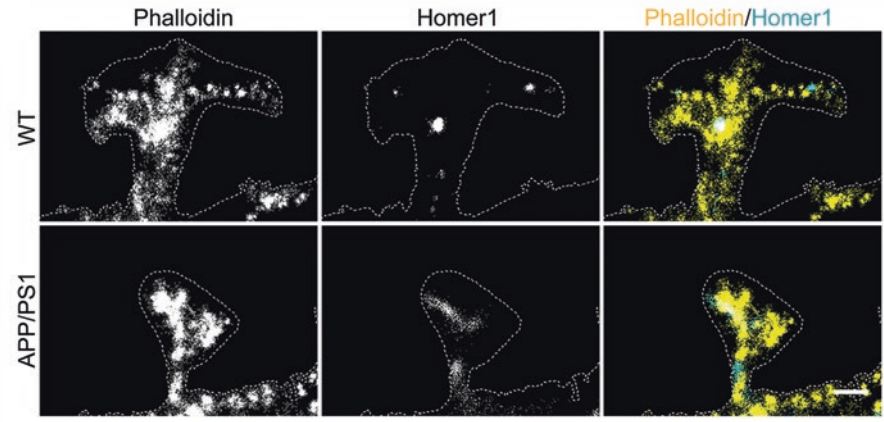

Fig. 9.29 β-amyloid mediates F-actin disassembly in dendritic spines leading to cognitive deficits in Alzheimer's disease (AD). Mushroom spines can be recognized by their characteristic morphology and the intraspine presence of Homer1 puncta and actin (merged images shown, respectively, in cyan and yellow on the right). F-actin labeling can be performed with Alexa Fluor 647-phalloidin. In addition to the detection of actin rods, it is also possible to determine whether the fibers are parallel to each other. Accordingly, mushroom spines were selected to study radiating actin structures within the spine head in a transgenic (APPswe/PS1ΔE9, APP/PS1) mouse model of AD. Mean anisotropy values were compared between wild-type (WT) and APP/PS1 mice to quantify changes in F-actin organization. Direct stochastic optical reconstruction microscopy revealed the occurrence of F-actin depolymerization in dendritic spines, which is causal and not consequent to decreased spine density in AD and leads to a breakdown of the nano-organization of outwardly radiating F-actin rods in primary cortical neuronal culture. (Legend adapted and figure reprinted from Kommaddi et al. (2018) under CC BY license and Copyright Kommaddi, Das, Karunakaran, Nanguneri, Bapat, Ray, Shaw, Bennett, Nair, Ravindranath; doi: 10.1523/JNEUROSCI.2127-17.2017)

dysregulation of spine dynamics in neuropathologies (Runge et al. 2020), which can also support predictive models aiming for novel therapies for neurological and psychiatric disorders (e.g., Paoletti et al. 2013; Beutel et al. 2020; Hunt et al. 2022).

These morphological data would then help to elaborate how specific cells bring about different functional outputs and a broad repertoire of responses from a multitude of axonal inputs arriving at the same brain area and cell. This complex task looks like finding the functional feature of each cell or brain area as a piece of a mosaic. One realizes that these neuronal and glial subpopulations in different organized circuits and timely interconnected areas function as a synaptically coded and responsive "orchestra" able to perform various meaningful "symphonies". Each node (and there are multiple nodes with intermingled subsets of cells, distinct neural temporal dynamics, and connectional strengths) receives "weighted" inputs to be integrated for an output code, both displaying a repertoire of flexible possibilities within the limits and properties of each circuit (Li et al. 2017; McCarthy 2023). At the cellular level, the number, spatial

distribution, and strength of each synaptic contact along a widespread receptive field are modulated by the interaction of each axon upon dendritic segments and pleomorphic spines. Perpendicular axons may establish few contacts with the dendrites of one neuron but may contact many neurons; otherwise, parallel projections may selectively innervate a few neurons and strongly influence these targets (Yuste 2010). Together, the "orchestra" plays with the activity-dependent intensity and source of inputs combined with variable amplitudes of functional output codes from the embedded components. Graded "ups" and "downs" of cellular excitability all over time mean that cells and areas will be activated, and others will be less activated or even deactivated (Newman 1999; Fig. 9.30a). These dynamic switches form different codes that represent the interpretation of what is being processed (Busler et al. 2019; e.g., see functional data from young men submitted to sexually arousing films in Redouté et al. (2000)and neural correlates of romantic love and affection in women and men in Zeki (2007), Acevedo et al. (2012), de Boer et al. (2012)). Dendritic spines are part of this scenario modulating excitatory neural processing and elaborating the initial steps for these output codes. It is expected that different types of cellular and network computations manifest with different time-series features of coordinated gradients of activity within and between brain areas (Shafiei et al. 2020). In the end, these functional codes established by interacting neural populations "sound" as different instruments being played by musicians in an orchestra. The sequence and intensity performed by each "group of instruments" are determined by the connectivity of their elements under a formidable functional and temporal fine-tune (Fig. 9.30b; see also Fig. 9.3 in Leopold et al. 2019 and further recent data on brain networks).

Species-specific interpretation of the "world," (un)conscious elaborations, memories and learning possibilities, emotions, and social behaviors depend on the distributed and coordinated activity of these neural populations, their codes at multiple spatial and temporal scales, and the integration of information in local and long-range networks. The interconnection of elements can be extensive within circuits (Fig. 9.30b; Glasser et al. 2016) progressing toward eventual "actions" in a multimodal integrated organization (Bruton 2021; Kolb and Whishaw 2021). Under physiological conditions, these actions emerge from a dynamic pattern of activation across the network rather than an "on" or "off" state of any one of its nodes (Newman 1999). A sequence of behaviors relates to a particular temporal pattern of activity of associated areas in the whole network (Fig. 9.30a), and subtle changes in this activity would mean different states and emergent properties, such as the few microvolts that evoke different firing rhythm patterns of thalamic relay neurons coding slow-wave sleep or wakefulness (McCormick and Pape 1990). In this same regard, cortical motor neurons are activated when processing information by observing or executing movements in rhesus macaques. However, rather than existing functionally distinct subpopulations of cells to perform these activities, motor neuron populations exhibit both a commonly shared computation and a unique task-dependent and dynamic coordinated temporal activation for one or another action (Jiang et al. 2020). At this point, an outstanding question is how microscopic-level neural

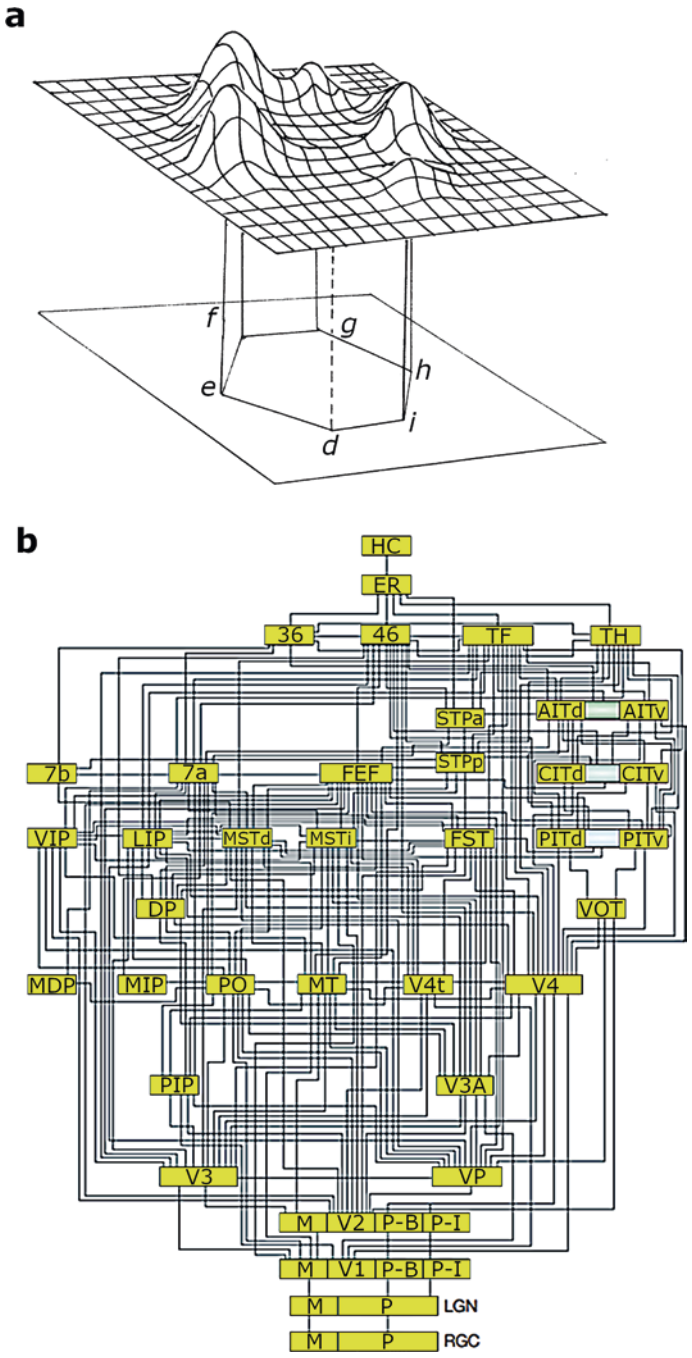

Fig. 9.30 (**a**) A hypothetical three-dimensional graph representing the magnitude of activation or inhibition/deactivation of integrated brain areas. These areas are organized as a functional network for the display and to modulate homeostatic activity or behaviors. Areas are indicated by letters (*d-i*) at the bottom of the image. The present synchronous pattern of activity represents an output code in the network and will determine a specific response. Changing the spatiotemporal ampli

coding mechanisms interact with macroscopic scale aspects for evoking our most complex neural circuitry activities, including consciousness, abstract thoughts, creativity, and feelings (Creutzfeldt 1995; Timo-Iaria and Valle 1995; Panzeri et al. 2015; LeDoux and Brown 2017; see an interesting discussion on perceiving itch or pain using multiple combinatorial codes from the same sensory receptors in Gardner, 2021).

The intra-individual and interindividual differences associated with the structural plasticity of human neurons, dendrites, spines, and synapses imply a large repertoire of computational possibilities for the human brain. Cellular morphology provides clues for functional implications of local connectivity and the levels of information processing, and a foundational knowledge that is continuously refined as new information is acquired (adapted from Rust and LeDoux 2023). Moreover, basic morphological data can be associated with probabilistic cytoarchitectonic maps and 3D-reconstructed images to interpret ultra-high field fMRI results in normal and pathological conditions (Kiwitz et al. 2022). Spines evolved to expand the plasticity of networks' functioning as miniature elements with multi-integrative capacity (Yuste 2010). It is not surprising that the number of cells and the level of complexity of the human cerebral cortex reflects its capacity to execute over 1.2 Zetta logical operations per second (Georgiev et al. 2020). Unraveling the dynamic role of dendritic spines for synaptic processing in humans is a task that needs multiple complementary experimental approaches linking morphology to physiology. This endeavor currently resides on the astonishing scale of around 10^{15} connections in the human brain (Rasia-Filho 2022; contextualized by DeWeerdt 2019). Nevertheless, spines can provide varied modulatory possibilities for synaptic transmission serving homeostatic and flexible requirements, showing a varied number and shape with phylogenetic and ontogenetic implications for network performance, and providing relevant cues to be investigated in human neurological and psychiatric conditions.

Fig. 9.30 (continued) tude of activity of one or various components would change the resultant output code and, consequently, evoke a different response display. (Figure reprinted and slightly modified from Newman (1999) under CCC RightsLink® license #5438910072828, originally published by John Wiley and Sons). (**b**) Multiple, intertwined streams for visual processing in the primate cerebral cortex. From the bottom to the top, visual areas and other associated nonvisual areas are indicated by rectangles (highlighted in yellow) and connecting pathways by lines, most of which are reciprocal ones. This schematic representation includes magnocellular (M) and parvocellular (P) retinal ganglion cell (RGC) and layers of the lateral geniculate nucleus (LGN) as the afferent pathway to visual area 1 [V1, with further split into the parvo-blob (P-B) and parvo-interblob (PI)], progressing sequentially to neighbor visual cortical areas (V2, V3, VP, and on) plus nonvisual areas [BAs 7a and 7b, perirhinal area 36, middle frontal area 46, entorhinal cortex (ER), and hippocampal complex (HC)]. Note the connectional complexity of such circuitries and the possibility of feedback and feedforward loops affecting the dynamics of information processing within it. It is important to include spines and synapses needed in each step for the elaboration of memories, emotions, social judgments of facial expressions, and empathy, for example. (Figure reprinted and slightly modified from Felleman and Van Essen (1991) under CCC RightsLink® license #5438980718898, originally published by Oxford University Press)

Fig. 9.31

P.S.1: "To write is to weave" (Eduardo Galeano) to transform imagination into symbolic representations of words. Imagination also makes us prone to find "dendritic spines" (and a "PSD" indicated by an asterisk) in unsuspected places (Titiqaqa Lake, border of Perú and Bolivia, seen from a plane window; Fig. 9.31).

P.S.2: Last but not least, the authors are thankful (and dedicate this chapter) to all persons who donated samples from their beloved relatives for the study of the human brain by scientists they may have never known before. Our gratitude and respect are due not only because of such an altruistic attitude while grieving but also to their deep trust in science and the best future for other persons and our humanity.

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