Opinion

Evolution of cortical neurons supporting human cognition

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Human cognitive abilities are generally thought to arise from cortical expansion over the course of human brain evolution. In addition to increased neuron numbers, this cortical expansion might be driven by adaptations in the properties of single neurons and their local circuits. We review recent findings on the distinct structural, functional, and transcriptomic features of human cortical neurons and their organization in cortical microstructure. We focus on the supragranular cortical layers, which showed the most prominent expansion during human brain evolution, and the properties of their principal cells: pyramidal neurons. We argue that the evolutionary adaptations in neuronal features that accompany the expansion of the human cortex partially underlie interindividual variability in human cognitive abilities.

Cortical neurons as the principal building blocks of cognition

Compared with other animals, human cognition clearly stands out. Many species can display very intelligent behavior, typically tuned to their ecological niche. However, human brains are capable of developing unique cognitive skills (e.g., sharing and storing information through symbolic language), without which human civilization would not be possible. For thousands of years, one of the most fundamental questions in philosophy and neuroscience has been the biological origin of human intelligence. What neurobiological principles underlie the cognitive abilities of the human species?

A major development in the evolution of the mammalian brain is the immense expansion of the neocortex [1]. The neocortex supports the higher cognitive functions that characterize humans. Relative to the total brain size, the human cerebral cortex is the largest among mammals, its grey and white matter occupies 75–82% of the entire brain mass or volume [2] and has a noticeably larger number and size of gyri [3]. Larger cortices also contain more neurons and thus more computational units to process and store information. A comparison of the cognitive abilities of 75 species of mammals and birds demonstrated that the number of neurons in the cortex or **avian pallium** (see Glossary) correlates with measurements of cognition [4].

However, compared with other primates, the increase in both brain size and the number of neurons in humans is 'remarkable, yet not extraordinary' [2] and the key to the puzzle of human cognition should not be sought solely in the overall brain or cortical anatomy. In fact, the human brain has just the number of neurons that would be expected for a primate brain of the same size [2]. Furthermore, frontal cortices that are often linked to human cognitive advantage (although relatively and **non-allometrically** expanded compared with most mammals [5]) are not disproportionately large in humans [6,7]. Moreover, across most mammalian species, including humans, cortex invariably

Highlights

Cortical expansion in humans might be driven by changes in neuronal properties and connectivity rather than sheer increase in neuronal numbers.

Recent breakthroughs in large-scale transcriptomic analyses of cortical neurons make it now possible to identify the genetic signature of neuron types and compare neuronal properties across species.

Human upper cortical layers contain neurons with large and complex dendrites that allow a single human neuron to perform computations similar to a multilayered network.

Strong and reliable synapses that recover quickly from synaptic activity, and fast signaling properties, help these neurons efficiently process information.

Several neuronal features of human neurons, such as dendritic size and complexity and fast signaling properties, also associate with cognitive ability in human individuals, supporting the link between neurons and cognitive function not only between but also within species.

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contains 20–25% of all brain neurons, even though the relative size of the cortex can reach 82% in humans [2].

Hence, cortical expansion and associated increases in cognitive ability might reflect changes in neuronal and non-neuronal properties rather than changes in the sheer number of neurons. Our brains function through the activity of almost one hundred billion neurons and their connections, which form the principal building blocks for the coding, processing, and storage of information in the brain, ultimately giving rise to cognition. Given the astronomic number of neuronal connections, in the order of 10^{14} to 10^{15} [4,8], even the slightest changes in the efficiency of information transfer by neurons can translate into a large impact on the overall computational power of the brain.

Accelerated evolution of the human brain took place at all scales of brain organization: at the scale of genes [9], genetic regulation [10], synaptic proteins [11], and lipids [10], influencing how neurons [12], networks [13], and brain connectivity [14] evolve. The overall result of this multiscale evolutionary process is not only increased cortical volume but increased diversity and complexity in the structure and function of cortical neurons and their synaptic connections. Thus, the speed and efficiency with which we accomplish cognitive tasks might be rooted deeper in the hierarchy of brain structure and arise from the characteristics of its basic elements: cortical neurons [15–18].

Do human neurons have specialized properties? Recent advances in large-scale single-cell transcriptomics of human cortical neurons, as well as the identification of human neuron types, physiological, morphological, molecular, and connectivity properties, allow us to answer this question. [19–21]. By comparing human cortical neurons with those of other species, evolutionarily conserved neuronal cell types and features can be distinguished from those unique to humans.

In this review, we discuss the evolution of the human brain from the vantage point of single cortical neurons and their local circuits. We attempt to answer how the evolutionary increase in brain size and complexity is linked to adaptations in the structure and function of human cortical neurons. We put forward the hypothesis that neuronal properties may partially explain the observed gap in mental ability between humans and other species and provide an overview of the recent evidence for this. We focus primarily on the adult **pyramidal neurons**, the most abundant cortical neuron type, but acknowledge that other cell types and neurotransmitter systems [22,23] likely also contribute to human cognition. We also acknowledge that evolutionary changes in the developmental timing of cortical neurons and **synapses** play an important role in the evolution of human cognition. Although this topic falls outside the scope of this review, we would like to point the reader to excellent recent reviews [24–26]. Finally, the focus of our review is on the pyramidal neurons of supragranular layers, as the morpho-electric properties of these neurons are more extensively studied in human cortex compared with deeper layers.

Cortical expansion is accompanied by changes in pyramidal neuron structure

Comparing cortical structure across multiple orders of mammalian species [27–29], including primates [30], reveals that not only does the cortical surface and **gyrencephalization** increase in larger animals, but also cortical thickness tends to increase with brain size, while neuron densities decrease [1,31,32]. Although the mammalian neocortex has a similar six-layered structure (Box 1), across the neocortex there are substantial variations in the thickness of these layers and overall cytoarchitectonic organization. This variation reflects the functional role of cortical areas [33,34]. As sensory information flows from primary sensory areas to progressively more integrative areas in temporal and parietal lobes [35,36], more complex features of sensory stimuli are combined along the way to finally create a complex mental representation. Similarly, cortical and laminar structure follows this functional hierarchy [33]. From sensory

Glossary

Apical: the main dendrite extending to L1 and the surface of the cortex from neurons located in deeper layers.
Avian pallium: the layers of grey and white matter that cover the upper surface of the cerebrum in birds; in mammals pallium is referred to as cerebral cortex.
Axons: long projections that originate at the cell body of a neuron and conduct electrical signals (action potentials) to other neurons.
Cortical (micro)circuit: two or more synaptically connected neurons that can collectively produce a functional output.
Dendrites: tree-like processes of neurons that are specialized in receiving synaptic information through synapses.
Dendritic excitability: the readiness of synapses and branches in a dendritic tree to respond with a positive change in membrane potential (depolarization).
Dendritic (calcium) potential: depolarization of the dendrites caused by the influx of ions through the activation of voltage-gated channels or receptors.
Depression: the progressive reduction of the postsynaptic response.
Facilitate: show facilitation, an increase in synaptic efficacy.
Gigantopyramidal Betz cells: giant pyramidal neurons located within L5 of the primary motor cortex, the largest pyramidal neurons within cortex.
Gyrencephalization: cortical folding.
Non-allometrically: deviating from the expected relationship of volume to body mass.
Presynaptic: the neuron that releases neurotransmitters.
Postsynaptic: the neuron that receives neurotransmitters.
Pyramidal neurons: principal excitatory neurons of cerebral cortex and hippocampus.
Short-term plasticity: a temporary change in synaptic efficacy caused by the history of presynaptic activity.
Soma: cell body.
Spine: a small protrusion on the dendritic membrane where synaptic connection (synapse) is formed.
Synapse: junctions that allow a neuron to electrochemically transmit a signal from axon of one cell to the dendrite of another cell. Inhibitory synapses decrease the likelihood of firing action potential, while excitatory synapses increase its likelihood.

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Box 1. Cortical organization and cortical neurons

In mammalian species, including humans, cortical neurons are arranged into a six-layered structure [1,8,47]. Cortical layers 2–6 (L2–L6) contain predominantly (70–80%) pyramidal neurons, the principal projection neurons of the cortex. They accumulate and integrate synaptic information on their vast dendrites and pass it on locally or to other cortical and subcortical areas through excitatory synapses. Although the principal load of information transmission lies on pyramidal neurons, their activity is strongly regulated and shaped by a diverse population of local inhibitory interneurons [8].

The broad structural characteristics of pyramidal neurons are similar across species: these neurons consist of a pyramidal-shaped soma that gives rise to apical and basal dendrites. The apical dendrite is orientated towards the cortical surface and ends in a distal tuft, while basal dendrites extend radially towards deeper layers.

The stereotypical organization of the cortex in a laminar structure has long tempted neuroscientists to derive generalized rules for connectivity. L1 contains mainly dendrites and **axons** of neurons from other layers and a sparse population of interneurons to regulate the inputs [101]. Based on neuroanatomical and physiological evidence, the upper supragranular layers, L2/L3, are thought to be the place where most recurrent computation happens: L2/L3 pyramidal cells have many re-excitatory connections, preamplify information, and send it to pyramidal cells in deeper output L5/L6 [102]. L3 pyramidal cells are also the main source of the feedforward projections to other cortical areas and receive recurrent input from other local superficial and deep pyramidal cells. L5 pyramidal cells are part of both direct thalamocortical and cortico-cortical microcircuits and dictate output to subcortical structures [103].

Supragranular layers seem to play an especially important role in cortico-cortical connectivity in the human brain (see Figure 2 in main text). Relative to monkeys and other primates, in humans there is a progressive shift of the laminar origin of connections from deeper (L5/L6) to upper layers (L2/L3). The result is that within human cortex a larger proportion of cortico-cortical connections originate from the supragranular layers [44]. These layers are also proportionately thicker in the human cortex compared with other primates [46], supporting a more important role of these layers in the integration of cortical information.

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to more integrative cortical areas, there is a gradient of increasingly thicker cortex [37] (supported mostly by layers 3 (L3) and 5 (L5), which contain large pyramidal neurons [38]), larger neurons with more complex dendritic arbors [39,40], and greater number of dendritic **spines** for synaptic contacts [41] (Figure 1). The larger pyramidal neuron size in larger brains across species is particularly pronounced in higher-order association areas [12,40,42]. Even the **gigantopyramidal Betz cells** in primary motor cortex, although having a larger **soma** and covering a larger cortical volume in big cats, have the most complex **dendrites** and longest total dendritic length in primates [20,28]. Yet, cortical synapse densities remain relatively constant, resulting in humans having the highest number of synapses per neuron [12,30,43].

Such gradients most likely represent increases in intracortical connectivity. In the human cortex, supragranular cortical layers, L2 and especially L3, contain large pyramidal neurons that send and receive predominantly cortico-cortical connections [44,45]. These layers are proportionally the thickest in humans (~50%) followed by other primates (46%), carnivores (36%), and then rodents (19%) [46], suggesting distinctions between species in the proportion of cortex devoted to cortico-cortical connectivity (Figure 2).

What effects do cortical expansion and increased connectivity have on the morphology of pyramidal cells? Neurons connect by making synaptic contacts on their dendrites, the larger the dendrites the more physical space for potential connections. The most distinctive feature of human pyramidal neurons compared with mouse and macaque pyramidal neurons is the size and complexity of their dendrites [19,47]. On average, human supragranular neurons are three times larger compared with mouse [47] (Figure 3, Key figure). Importantly, the larger human neurons are not simply upscaled rodent neurons: they have a more complex structure with longer dendritic terminals [47,48]. The elongation of terminals might reflect the extended period of cortical development and dendritic growth in humans, whose L3 pyramidal dendrites continue to branch and grow throughout childhood and adolescence [49].
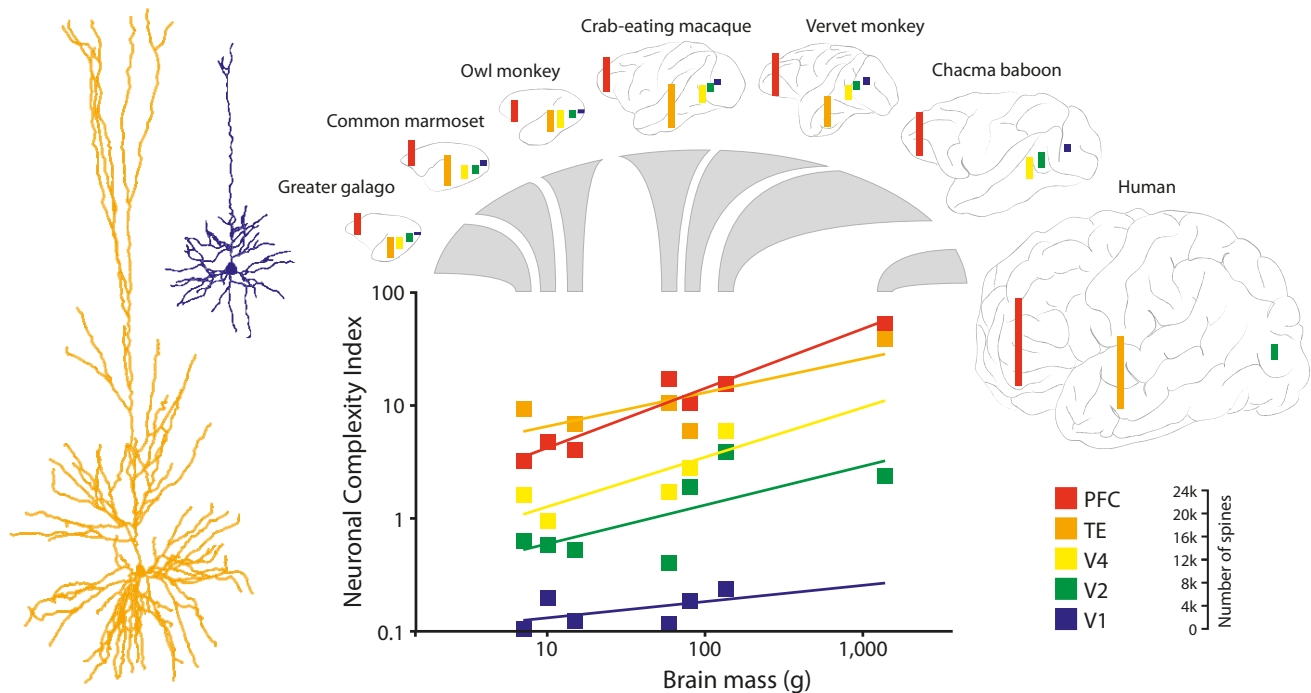
Figure 1. Gradients in the complexity of pyramidal neurons and their spine numbers. Gradients follow the functional hierarchy of cortical areas in primate species: neurons at the top of the hierarchy in prefrontal cortex and temporal lobe have the highest complexity and spine number. Neuronal complexity increases both across brain areas within a primate species and with brain mass across species. Two example L3 pyramidal neurons from the primary visual area (blue) and the inferotemporal cortical area (orange) from macaque monkey are shown left (modified from [39,40], image from Verhoog, M.B, PhD thesis, Vrije Universiteit Amsterdam, 2016). The height of the colored bars drawn inside the brain areas in the brain cartoons reflects the number of spines found on neurons, scale bar is depicted in the bottom right corner. Abbreviations: PFC, prefrontal cortex; TE, inferotemporal cortex; V1, primary visual cortex; V2, secondary visual cortex; V4, visual area 4.

Recent advances in single-cell transcriptomics make it possible to combine gene expression analysis (transcriptomics) of neuron types with detailed morphological and electrophysiological characterization [19,50]. Such analysis revealed another distinctive feature of L2/L3 pyramidal neurons: the increased diversity in dendritic structure, gene expression, and physiology between and within neuron types [19]. Based on transcriptomic signature, L2/L3 pyramidal neurons in human temporal cortex can be divided into five neuron types, named after their most distinctively expressed gene: *LTK*, *GLP2R*, *FREM3*, *CARM1P1*, and *COL22A1* [19] (Figure 3). Deep L3 neurons, *FREM3*, *CARM1P1*, and *COL22A1*, are of particular interest. Firstly, *FREM3* is the most abundant type in human cortex and shows the highest diversity in molecular, physiological, and structural properties that follow the gradient from more superficial to deeper cortical neurons [19]. Secondly, *CARM1P1* and *COL22A1* do not have homologs in mouse and might be a more recent evolutionary addition to the human cortex. Finally, large L3 neuron types *CARM1P1* and *FREM3* are immune-responsive to neurofilament protein marker SMI-32, which marks mammalian pyramidal neurons preferentially forming long-range cortico-cortical projections. These SMI-32-positive neurons were found to be selectively lost in Alzheimer's disease [19,51]. The fact that these cells are only found in human cortex and are vulnerable to a disease marked by cognitive deterioration emphasizes the link of the large L3 neurons to human cognition.

Furthermore, on the subcellular level, human dendrites also show more variability in spine size and density compared with other primate and rodent species [40,43,52]. Human spines are

(A)

HUMAN (MTG)

MOUSE (TeA)

L1
L2
L3
L4
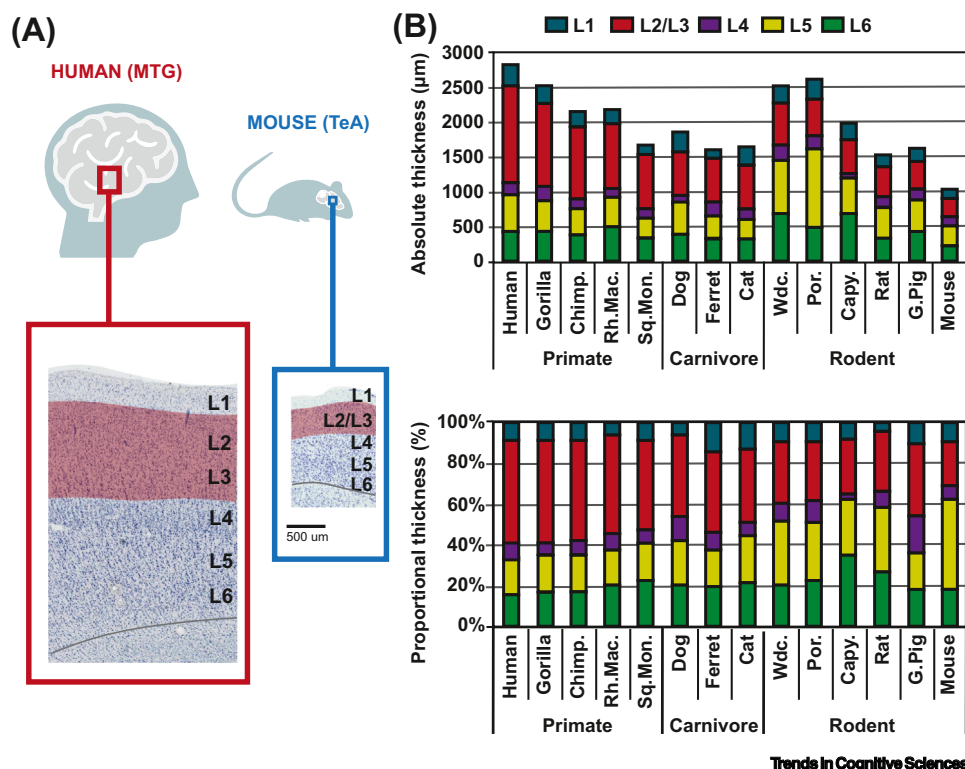L5
L6

L1
L2/L3
L4
L5
L6

500 um

(B)

Figure 2. Cortical expansion of the human brain. (A) Human and mouse brains differ in size and cortical thickness: histology images of two comparable cortical areas in human [middle temporal gyrus (MTG)] and mouse [temporal association area (TeA)] show proportionally larger supragranular layer in human. Images from © 2010 Allen Institute for Brain Science. Allen Human Brain Atlas. Available from: human.brain-map.org. (B) Supragranular layer thickness is larger in human cortex than other species, both in absolute size (top) as well as relative to the other cortical layers (bottom) (adapted from [46]).

larger, longer, and more abundant along the dendrite [43,52]. In particular, the **apical** dendritic tree shows more complex morphology, carrying bigger spines distributed more densely over the dendrite [53]. Because the apical tree is the biggest contributor to the total dendritic length of a neuron, the absolute number of spines is consequently also larger [53]. The morphology of dendritic spines is important since it directly influences the function of neurons [54]: the size of the spine corresponds to the number of receptors and therefore the ability of the neuron to receive inputs from surrounding cells. In particular, **presynaptic** active zones and **postsynaptic** densities have been reported to be larger in human neurons [55–57], suggesting the synaptic connections are also functionally stronger. Finally, since larger spines are more stable and long-lasting, fluctuations in spine volumes might mirror the psychological properties of complex behaviors such as memorizing and forgetting [58].

Thus, human neurons have more complex and larger dendrites compared with other mammalian species and also more diversity within neuron types. Long dendrites not only physically contain more space for potential synaptic contacts but also have more abundant and larger spines. In addition, dendritic complexity and spine numbers increase in brain areas with higher cognitive load, suggesting that more complex neuronal morphology reflects a more complex cortical function. Taken together, the morphological features of human neurons point to a larger repertoire of information processing patterns that human dendrites can process.

Key figure

Cortical expansion is accompanied by adaptations in pyramidal neuron morphology
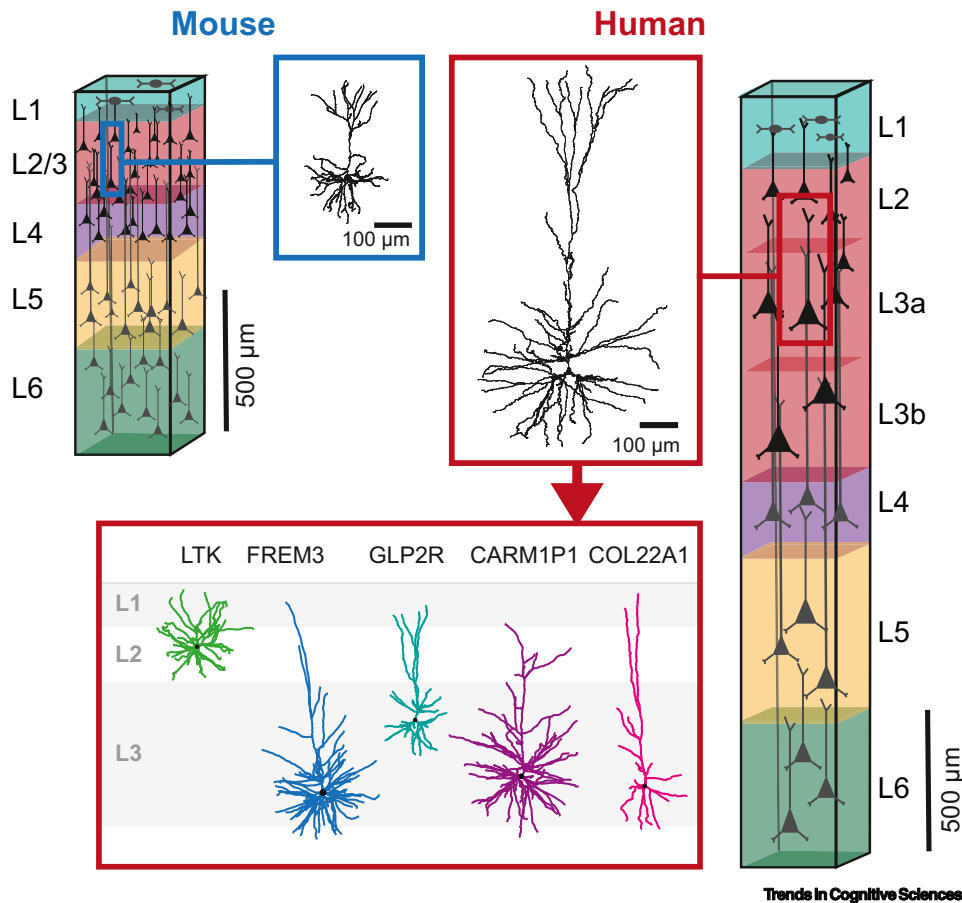

Figure 3. Increased layer 2/layer 3 (L2/L3) size is accompanied by changes in cytoarchitecture of cortical layers and morphological properties of neurons. Human L2/L3 neurons have threefold larger and more complex dendrites than mouse or macaque and contain a larger diversity in transcriptomic excitatory neuron types. In mouse cortex, L2/L3 contain three distinct transcriptomic types with relatively compact dendritic morphology and cell body location strictly adheres to layer boundaries. In contrast, human cortical layers 2 and 3 contain five transcriptomic types that show strong diversity in dendrite morphology, with several large dendrite neuron types that are not found in rodents (based on the data from [1,19,47]).

Complex dendrites increase the computational repertoire of single neurons

Neurons process information by integrating thousands of synaptic inputs on their dendrites. The increased size and complexity of dendritic trees offer a greater diversity for computation. Dendritic branches may act as individual processing units and perform distinct computations independently. Thereby, a single neuron can perform similarly to a network of several neurons. Indeed, detailed models of hippocampal and cortical pyramidal neurons demonstrate that these neurons behave computationally, similar to a network with multiple hidden layers [59,60].

Direct recordings from distal dendrites in human pyramidal neurons in neurosurgery brain tissue have recently confirmed these theoretical predictions and directly demonstrated that human dendrites act as separate processing compartments [61–63]. Human dendrites in supragranular pyramidal neurons were shown to be readily excitable, which was not observed in rodent L2/3 pyramidal neurons [64], and this **dendritic excitability** was mediated by **dendritic calcium potentials** [62]. Importantly, the dendritic responses only occurred in response to a highly selective window of input strength. If that window is exceeded, the response to additional synaptic input drops off. This mechanism acts as an anti-coincidence detector: a single, sufficiently large dendritic input is amplified and passed on to the soma, while multiple coincident (and thus larger when summed) inputs are canceled. In this way, single human pyramidal neurons can perform logical operations such as 'exclusive or', converting one or the other input, but not both, previously thought to require multiple neurons [62]. Thus, human pyramidal neuron dendrites may possess a different logical operator repertoire, which could alter cortical computation by allowing dendrites to process inputs more independently. Finally, dendritic electrogenesis has also been observed in L5 human pyramidal neurons [61,63,65], though underlying mechanisms might deviate for different cell types [63] (Box 2).

Human neurons receive strong and reliable excitatory inputs

The computational advantages of large human dendrites bring significant challenges to neuron physiology. Because human supragranular pyramidal neurons have twice the number of synapses compared with mouse or rat neurons [8], many simultaneous inputs must be integrated and relayed over longer dendritic distances to generate output in the distant cell body. How do human neurons cope with this challenge and process multiple signals without information loss?

Apart from dendritic amplification by calcium action potentials (APs), human synaptic connections differ from those of rodents in their strength and dynamics. For instance, human excitatory

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Box 2. Properties of human L2/L3 versus L5 pyramidal neurons

The diversity of human neurons and their properties is not limited to supragranular layers of cortex [19] but extends to deeper layers such as L5 [63,104]. In fact, for most physiological features, human L5 neurons show even larger heterogeneity across neurons and types than across species [63]. Several studies have recently compared the physiological properties of human neurons across and within layers [19,63,104]. Human L5 pyramidal neurons were the most excitable and exhibited the most prominent HCN-channel-related membrane properties, such as increased I_h, sag current, and resonance gain at delta and theta frequencies [104].

L5 pyramidal neurons can be divided into two broad classes: intratelencephalic-projecting (IT), which send axons to targets within telencephalon, and extratelencephalic-projecting (ET), which also project to subcerebral targets and thus control cortical output [105]. Using transcriptomic information to identify human IT and ET types, ET neurons were revealed to be surprisingly sparse in human cortex (2–6%) compared with rodents (20–30%), but their morpho-electric properties and gene expression profiles are as distinctive as their rodent counterparts [63]. Morphologically, human L5 ET neurons, similar to rodent, have thick apical dendritic tufts, whereas L5 IT neurons are thin-tufted [63,106]. Electrophysiologically, in both rodent and human L5 ET neurons, HCN-channel-related membrane properties are enhanced compared with L5 IT neurons, especially at distal dendritic recording sites [61,63]. Moreover, human L5 ET neurons have fast AP kinetics and respond to near-threshold current injections with high-frequency AP bursts, a phenomenon that has been associated with dendritic Ca^{2+} electrogenesis. Indeed, dendrites of L5 ET neurons were shown to have strong electrogenesis, suggesting that human L5 ET neurons possess active mechanisms capable of generating dendritic spikes [63]. In contrast, other reports showed that human L5 neurons have lower electrogenesis in distal dendrites compared with L5 neurons of other mammalian species, including rodents, rabbits, marmosets, and macaques, and thus increased computational compartmentalization [61,65]. In particular, potassium and HCN currents were lower than expected based on the size of the human L5 neurons. The discrepancy between the studies can partly be explained by the recordings at different dendritic locations and possible differences in targeted subtypes of L5 neurons, but other mechanisms might also be involved.

Thus, similar to supragranular layers, human L5 neurons demonstrate both conserved functional properties across species as well as high phenotypic diversity that could reflect increased functional specialization of human cortex.

synapses have threefold larger synaptic vesicle pools and presynaptic active zones compared with rodents [55,56], resulting in larger synaptic currents in individual connections [55]. Excitatory synapses are not only stronger in humans, but they are also more resilient to repeated activation [66]. In synaptically connected pyramidal neurons that fire repeatedly, the postsynaptic response in the receiving cell typically decreases as a result of synaptic **depression**. During such repetitive activity, depressing human synapses were shown to recover three times faster than those of mouse [66]. Rapid recovery from depression increases synaptic resolution and allows neurons to distinguish fast incoming inputs with substantially larger amplitudes for computation. Models based on rodent synapses predicted that depressing synapses perform optimally in response to very low frequencies of inputs [67]. However, because recovery from depression is so fast in human synapses, they can actually also transfer substantial amounts of information during trains of APs and high-frequency bursts [66]. As a result, human synapses can transfer up to nine times more information compared with rodents [66].

These findings were recently confirmed in several connectivity studies investigating connected pairs of neurons in mouse and human [68–70]. L2/L3 excitatory connections were stronger and more reliable in humans, with fast recovery from depression [68,70]. In particular, L3 neurons have the highest excitatory responses even compared with pyramidal neurons in other layers [68]. Notably, there is a gradient in the type of **short-term plasticity**: connections of more superficial L2 neurons **facilitate** (second response is greater than the first), while deeper L3 neurons show depression (second response is smaller) [68]. The facilitating connections have the highest impact during sustained high-frequency activity, while depressing synapses are the strongest during sparse firing. Thus, such a gradient may indicate different activity patterns of L2 and L3 neurons, with L3 neurons favoring sparse but strong activation. Finally, the observed connectivity rates and specific patterns of activity indicate a preferential one-directional routing of information from superficial (L2) to deeper layers (L3). In human cortex, this information flow can even be triggered by single APs in a subset of pyramidal neurons, which can initiate a cascade of complex, precisely timed events and recruit neuronal ensembles relevant to cognition [68,71,72].

Thus, synaptic dynamics in human pyramidal neurons are characterized by unique patterns of activity that can be triggered through highly reliable and strong excitatory synapses.

Mechanisms for overcoming large dendritic distance

Human pyramidal neurons need to convey synaptic inputs from very distal dendrites to soma. How do they achieve this? The shape of the dendritic tree and dendritic diameter might reduce the resistance in the dendrites and this might help to decrease the attenuation of the incoming synaptic signal, similar to water flowing with less resistance through a wider tube. Another mechanism was predicted by fitting cable models to short subthreshold membrane potential responses of human large L3 pyramidal neurons [73]. These neurons have reduced specific membrane capacitance compared with rodent pyramidal neurons, which facilitates dendritic signaling to the soma due to reduced capacitive charging currents. This property may be explained by differences in lipid composition of human cortical neurons [10]. Apart from the structural effects, dendrites might have active mechanisms to counteract the filtering of synaptic inputs: ion channels that are activated by changes in voltage and influence input transfer [74].

One of the most striking physiological differences between human and rodent neurons is the presence of a prominent hyperpolarization-activated nonspecific cation current, I_h, in human neurons [19,68,75]. This current is carried by hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which have high and ubiquitous expression in human supragranular excitatory neurons, but not in mouse neurons [75]. Computational modeling demonstrates that in

the presence of I_h, synaptic inputs arrive at the soma faster, with distal inputs in large L3 neurons benefiting the most from this mechanism [75]. Thus, HCN channels with their high density in the distal apical dendrites [76] may help large neurons to accelerate the transfer of distal inputs to the soma.

Converting inputs to outputs: fast and stable signaling helps to encode more information

The integration of synaptic inputs on human dendrites will ultimately determine whether the neuron will generate output: the firing of APs. Theoretical studies predict that the key determinant of computational speed in neuronal networks is the time neurons need to process inputs and convert them into neuronal output: AP signaling [77]. Recordings from human L2/L3 neurons show they are better able to maintain fast AP generation compared with rodents and that this might help them encode very dense synaptic information content [66]. AP generation speed is influenced by the large dendritic compartments of human pyramidal neurons, which act as a current sink and result in faster AP onset [78], but differences in voltage-gated ion channels might also play a role.

The ability of neurons to maintain faster AP speed may be especially important during high-frequency firing when neurons are engaged in cognitive tasks. Studies where single neuron activity was recorded in human subjects (usually by implanting recording electrodes in epilepsy patients as part of their treatment) typically report very low average baseline firing rates in cortical neurons (<1 Hz). However, during cognitive tasks, such as reading or learning, single neurons might increase their activity up to 30 Hz, which can last for minutes [79–81]. Human supragranular pyramidal neurons seem to be especially adapted to such activity and can maintain fast AP signaling at these frequencies much better than mouse neurons [82].

Furthermore, the combination of faster AP onset and faster recovery from synaptic depression allows human pyramidal neurons to track synaptic information at considerably higher frequencies. Even when inputs have a frequency of 1000 Hz, human neurons can reliably encode this information by timing their APs to the input, compared with the 200–300 Hz limit in rodent neurons [66]. Fast active properties allow human supragranular neurons to respond to inputs more quickly and therefore encode information at higher bandwidths and with higher temporal resolution [66].

Taken together, human neurons show physiological adaptations that might be linked to their increased size and complexity. Larger dendrites can act as separate computational compartments, but can also lead to faster AP onsets, have more HCN channels and I_h current, and can generate dendritic calcium APs. These characteristics enable neurons to boost and accelerate the transfer of inputs, allowing them to function similarly to a multilayered network. The increased computational power of single neurons may lead to advantages on the network level: fewer neurons are needed to encode a certain concept. Such sparse coding has enormous cognitive advantages because the same number of neurons can process more information [83]. Indeed, human concept neurons in the temporal lobe show an extraordinarily low sparseness of coding, in the range of 0.2–1% [84], compared with 33% for monkey temporal neurons [85,86]. Therefore, a shift in complex computation from networks to single neurons and even to dendrites might be a defining feature of human cortical evolution.

Cellular correlates of human intelligence

The evolution of cognitive functions that distinguish humans from other species is accompanied by cortical expansion and increased neuronal complexity. One might ask: are these neurobiological adaptations also relevant to human cognition? And could the same neurobiological differences also explain differences in cognitive ability between human individuals?

One of the strongest correlates of general intelligence that emerges from brain-imaging studies is increased cortical thickness and volume [87]. In multiple high-order association areas in temporal and frontal lobes, cortical thickness correlates with the outcomes of cognitive tests [87–92]. Since cortical function relies on the activity of neurons and connections on neuronal dendrites, interindividual variation in cognitive ability could express itself first and foremost at the cellular level. Do human neurons perform differently in individuals with higher or lower cognitive ability?

One way to approach this question is by measuring neuronal parameters in brain tissue from neurosurgery and correlating the findings to the results of preoperative cognitive tests. Before surgery, IQ tests are taken to assess various aspects of the patient's general cognitive ability, or general intelligence 'g', a measure that strongly correlates with educational attainment and socioeconomic status [93,94]. Using this method, it was recently shown that high IQ scores are associated with larger temporal cortical thickness containing pyramidal neurons with larger, more complex dendrites [16]. Based on the experimentally measured dendritic structures, model neurons showed that larger dendrites process rapid synaptic inputs with higher temporal precision [16], achieved by faster AP speed. Indeed, experimental recordings of AP firing in human supragranular pyramidal neurons showed that neurons from individuals with higher IQ scores were better at maintaining fast AP speed during neuronal activity [16]. These findings provide evidence that human intelligence is associated with specific neuronal parameters such as larger, more complex dendrites, faster APs, and more efficient synaptic information transfer.

In a follow-up study [95], the authors provided a more detailed microstructural analysis of cortical layers and showed that thicker cortex in subjects with higher general and verbal intelligence is due to the increased thickness of supragranular cortical layers (L2/L3) only, while other cortical layers remain unchanged. The thicker supragranular layers did not contain more neurons, but rather larger cells at lower density (Figure 4).

Taken together, these studies provide evidence that higher cognitive ability in human individuals is supported by several cortical and neuronal features that are also favored by human evolution: thicker supragranular layers, larger neurons, complex dendrites, and faster signaling properties [95].

Concluding remarks

One of the primary driving motivations of neuroscience is to understand how the human brain processes information. Compared with other species, the human brain consists of large and complex neurons [47] that are capable of efficient information processing and fast-tracking of incoming inputs [73,82]. Moreover, the increased size of the dendritic tree can result in decompartmentalization between soma and distal dendrites, where dendritic branches become separate computational compartments processing diverse input patterns [61,62,96]. The human brain contains human-specialized pyramidal neuron types [19,21,97,98], but even types homologous to mouse show a larger diversity in physiology, morphology, and gene expression features [19,21]. In addition, microcircuit properties differ: human neurons show strong and reliable local connectivity with synapses that recover quickly from synaptic depression [55,69,82] and display unique forms of network activity [71].

Evolution-driven adaptations of the human cortex are remarkably similar to those that underlie differences in cognitive ability between human subjects. Overall brain volume and cortical thickness of association cortices, the hallmark of human evolution, are larger in subjects with higher cognitive performance [93,99,100]. Similarly, supragranular cortical layers, which expanded disproportionately during human brain evolution [45,46], are thicker in subjects with higher IQ [95]. The size and complexity of human dendrites are larger in human neurons [19,47] and also

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Figure 4. Cellular and cortical properties underlying interindividual differences in human intelligence. The well-documented association of cortical thickness of middle temporal gyrus (MTG) with IQ scores in healthy individuals [88,92,93] is driven by interindividual differences in the thickness of layers 2 and 3 (L2/L3) in human cortex that also associate with IQ scores. Subjects with higher IQ scores (right column in red boxes) have thicker L2/L3 that contains neurons with larger cell bodies at lower neuron densities, than subjects with lower IQ scores (left column in blue boxes). Pyramidal neurons in subjects with higher IQ scores (center red box) have larger and more complex dendritic trees and these neurons can maintain faster action potential (AP) rise speed during repeated firing than neurons in cortical L2/L3 of subjects with lower IQ scores (center blue box). Longer dendrites have more dendritic spines and have physically more room to receive synaptic inputs, thereby larger neurons can integrate more information from other neurons. AP shape stability supports fast neuronal information processing. Both factors are potentially contributing to cognitive ability and possibly drive the association of IQ scores with activity of MTG areas in fMRI ([93]; Figure based on the data from [16,95]).

associate with IQ scores [16]. Hence, increased cognitive performance in humans might result from the ability of large human neurons to perform faster computations and maintain fast AP speed during high-frequency firing [66] and, similarly, AP speed is faster in individuals with high IQ scores [16].

In conclusion, we are only beginning to understand how the broad spectrum of human cognitive abilities relates to neuronal function. New insights indicate that the evolution of human cognition and differences in cognitive ability might be driven by similar mechanisms at primarily the neuronal and microcircuit levels: increased cell size and complexity, more diverse computational repertoire, and distinct expression profiles of various genes within and between neuron types. Identifying conserved and specialized features of cellular organization and function in the human brain

and building theories of how they support human cognition is only the first step. The critical and challenging next direction is to formulate testable predictions (see Outstanding questions). Novel high-resolution techniques applied to human neurons might provide the necessary tools to face this challenge and directly test theories of neurons supporting human cognition.

Declaration of interests

No interests are declared.

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