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REVIEW

Human Cellular Neuroscience and the Uniqueness of the Human Brain

What makes the human brain special: from cellular function to clinical translation

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Abstract

What makes the human brain special? Human neurons, glia cells, and cortical circuits have been shown to be significantly different from those of other species, including mammals. This has led to a massive effort by the neuroscience community to directly study these differences in a multimodal approach. The studies conducted include single-cell and network recordings of human tissue samples, single-cell transcriptomics, and morphological analysis of the distinct cells to better understand the underlying differences from the cellular to the systems level. Furthermore, to overcome the translational gap from animal studies to patient care, the development of disease modeling in human tissue samples is of utmost interest. Here, we review and highlight research that focuses on the specialization of the human brain from molecular expression, cellular properties, to the challenges and promises of clinical translation.

cell types; cortex; epilepsy; glioblastoma; human brain

INTRODUCTION

Neuroscientific research is motivated by the hope that a better understanding of the cellular and systems-level mechanisms of the nervous system will help to explain human behavior, brain function, and pathogenesis, ultimately facilitating the development of effective treatments and cures of neurological and psychiatric diseases. Model systems, such as nematodes, insects, crustaceans, rodents, and certain cell lines and expression systems, have proven to be critical for providing fundamental insights into molecular, cellular, and systems neuroscience that also apply to other organisms. Yet, there is an increased realization that mechanistic insights into neuronal functions obtained in nonhuman organisms often fail to translate to the human brain. This becomes obvious in the failure rates of trials aimed at curing or treating human neurological disorders (1). However, it is important to emphasize that translational hurdles are not limited to the trial stage. For many conditions, currently approved treatments remain insufficient even after successful clinical implementations. For instance, in epilepsy, approximately one-third of the patients do not respond to existing antiseizure medications (ASMs), highlighting a persistent gap between mechanistic insight and therapeutic efficacy (2).

Although significant progress has been made in understanding the cellular mechanisms underlying brain tumors (3), neurodegenerative diseases such as Alzheimer's disease

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and Parkinson's disease (4–6), neurological disorders such as Rett Syndrome (7–9) and epilepsy (10), as well as the detrimental consequences of spinal cord injury or stroke (11, 12), there has been limited success in translating therapies or cures that are effective in model organisms (13, 14). The limited success of translating mechanistic insights obtained in animal models to the human brain and neurological and psychiatric diseases contrasts with the transformative results seen in other organs and diseases, such as many types of cancers (15, 16). There are multiple reasons for the challenges in translating findings from model systems to the human clinic, in particular with regard to neurological and psychiatric diseases (17–23). As for neurological and psychiatric disorders, a major contributing factor is the unique complexity of the brain. Unlike other organs, the brain consists of thousands of specialized neuronal and glial subtypes (24, 25). These subtypes possess specialized cellular properties and precise, context-dependent connectivity patterns. Neuronal activity is state-dependently modulated, context-specifically excited or inhibited, and homeostatically regulated. The cellular- and systems-level characteristics of all brains must be uniquely adapted to the animal's behavioral, developmental, and environmental needs and thus differ from species to species.

In humans, this has given rise to particularly specialized traits, including complex language with syntax and grammar, advanced forms of self-reflection, long-term planning, and autobiographical memory (26–28). Although elements of symbolic thought and social cognition are clearly present in other species (29, 30), humans display a unique integration and expression of these capabilities, such as in the creation of representational art in the form of paintings and music, and abstract scientific reasoning. Thus, it should come as no surprise that many aspects of the human brain differ from those of even their closest relatives.

Features observed specifically in humans have been identified across all levels of neuronal organization, from molecular and cellular properties to large-scale systems architecture. These differences have direct practical consequences. For example, viral vectors that have been developed to specifically target certain cellular subtypes in a nonhuman primate (NHP) may fail to recognize this cellular subtype in the human brain (31–33). It is also unclear to what extent a given cellular subtype in a rodent or nonhuman primate even exists in the human brain (34, 35). Moreover, even if disease-driving cellular or molecular mechanisms have been identified in human patients, it is far from obvious how these mechanisms will impact neuronal subtypes and circuit interactions in the human brain. A lack of subtype specificity is a major challenge when attempting to apply precision medicine that relies on targeting specific inhibitory or excitatory neuronal subtypes implicated in a human disease. Insufficient specificity can lead to off-target effects and severe side effects. These unknowns and uncertainties are major obstacles in the development of effective treatment strategies, such as gene therapy that targets diseases of the human central nervous system (CNS).

To gain an understanding of humans' unique cognitive capabilities, such as human intelligence, global connectivity studies using fMRI technology have been successfully implemented. In addition, to bridge all levels of integration, it is also important to study cellular properties in human tissue. Only in humans it is feasible to show that in brain regions associated with cognition, cellular properties can vary individually with intelligence. This is reflected, for example, in differences in the rise speed of action potentials (APs) and the dendritic morphology of pyramidal neurons (36, 37).

Also, when it comes to understanding human disease, such as seizure dynamics underlying human epilepsy, it is critical to bridge cellular-, network-, and system-level properties that span from in-depth analysis of resected human tissue to EEG characterizations, which may vary individually from patient to patient (38, 39). These differences may be critical to explain the variability in the clinical response to ASMs. This requires a personalized approach in which data from measurements in vivo are combined and compared with the cellular properties determined ex vivo from the same individual.

Although human brain tissue models offer promising avenues for studying disease mechanisms and drug responses, several limitations remain. These include a lack of knowledge regarding cellular integrity and viability in slice cultures over extended periods, cellular and molecular heterogeneity within tissue samples, and limited scalability due to restricted availability of human material. In addition, variability among patient-derived samples poses challenges for reproducibility and control comparisons.

A limited number of studies have already used human organotypic slice cultures to study network function (40, 41), but further studies will be necessary to determine the validity and stability of the approach.

Importantly, the validity of ex vivo human brain models for assessing preclinical drug efficacy needs to be tested with known compounds before its use for novel candidates. Moreover, testing ASMs in vitro will only test its efficacy against induced or spontaneous "seizure-like activity," which differs fundamentally from seizures in a whole organism. This discrepancy may result in false negatives or false positives, as exemplified by levetiracetam, which shows limited efficacy in some in vitro seizure models (42).

Although this review emphasizes the importance of studying the human brain, ultimately, it comes down to finding the right model system for the right question. Clearly, animal models also have their unique advantages. In many situations, a simple model can be highly useful to answer fundamental questions, as has been shown many times in invertebrates (43).

Yet, the outlook to ultimately translate mechanistic cellular insights to the human brain and treat neurological or psychiatric disorders is not as bleak as these general considerations may suggest. There has been progress in developing gene therapy for several diseases, and much has been learned from the positive and negative experiences with targeted viral vector technologies (44–47). In addition, there are renewed efforts to focus on the study of the cellular and molecular properties that are specific to the human brain. This review cannot cover all aspects of human uniqueness and the approaches used to study the human brain. Although we focus on the cellular and clinical translation of human brain research, we recognize that ethical considerations are critical to this field. Issues such as informed consent, ethical procurement of human tissue, donor privacy, and compliance with

regulatory standards underpin all human studies and must be rigorously respected. For a comprehensive discussion of these topics, we refer readers to specialized literature focused on research ethics in human neuroscience. Our review will focus primarily on the cellular basis of the human brain and serves as a conceptual framework for a call for papers on the uniqueness of the human brain to be published in the *Journal of Neurophysiology*.

WHAT IS SO SPECIAL ABOUT THE HUMAN BRAIN?

Human Evolution and Specialized Genes

The human brain has undergone a striking evolutionary transformation that affected not only the neocortex but also areas such as the cerebellum. Various mechanisms, including the process of indirect neurogenesis, have been attributed to the development of the increased complexity of the human brain (48). An interesting concept is that the process of brain development and maturation is progressively slowed in the human lineage ("bradychrony"), which allows for an increased complexity and diversification of the cellular progenitor pool, increased brain size, cell number, subtype diversity, and connectivity (Fig. 1) (50). Several features in the three-dimensional (3-D) architecture of the human genome have undergone specialization. Human-specific topologically associated domains and human-specific loops seem to play a role in the subplate of the developing human brain (51). The genome of humans has been extensively altered by duplications, deletions, inversions, and translocations (52), and a recent study identified ~17,000 human-specific structural variants (53). Specific gene variants have been associated with human cognition, and many of those variants are expressed in higher-order cortical areas such as the middle temporal gyrus (36). Interestingly, the expression pattern of these variants can be correlated with intelligence quotient scores. Changes in expression patterns are also important for understanding human diseases, such as schizophrenia (54). Importantly, not only neurons but also the development of glial cells shows distinct differences in humans, and human-specific astrocyte genes have been described (35, 55, 56). For instance, WNT inhibitory factor 1 (*WIF1*), peripheral myelin protein 2 (*PMP2*), and glutathione S-transferase mu 2 (*GSTM2*) are astrocyte-enriched genes in humans but are not expressed in mouse astrocytes (35).

Finally, humans have evolved to use very specific and complex cognitive functions as compared with other mammals. Cognition and empathy are vastly amplified in the human brain compared with other species (57), as are language and the use of tools (58, 59). Some cognitive abilities, such as abstract thinking, are uniquely attributed to humans (60). Since all such activities rely on the core functions exerted by the cerebral cortex, specialized mechanisms are involved in its development.

The Development of the Human Brain

Across metazoans, tissues and organs develop in a way that enables specific functions. For example, compared with slow-running animals, muscles of fast-running animals develop differently to ensure explosive movements and accelerations

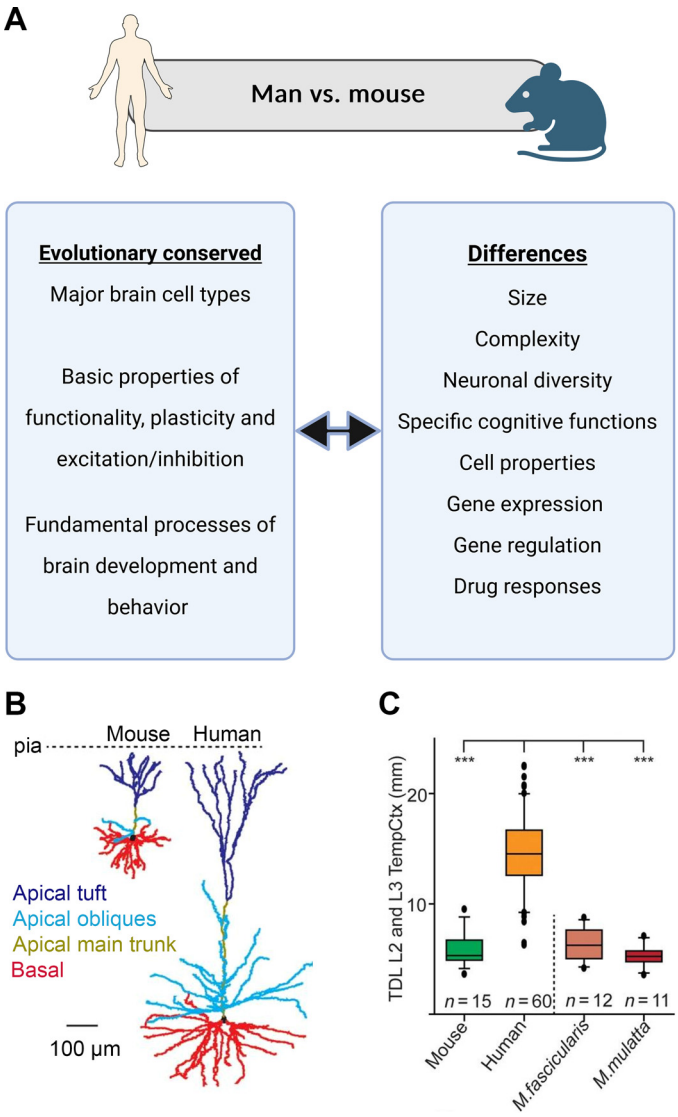

Figure 1. Man vs. mouse comparison of neuronal properties, size, and complexity. *A*: schematic overview of differences and evolutionary conserved properties comparing the human brain with the rodent brain. *B*: comparison of size and structure between a mouse and a human pyramidal neuron, apical tuft colored in violet, apical obliques in blue, apical main trunk in yellow, and basal dendrites in red. Scale bar = 100 µm. *C*: comparison of total dendritic length of neurons located in L2/3 of the temporal cortex between the human, the mouse, *Macaca fascicularis*, and *Macaca mulatta* (Kruskal–Wallis test, ***$P < 0.0001$). Figure adapted from Ref. 49; used with permission from Oxford University Press. Figure, in part, created with a licensed version of BioRender.com.

(61). This also applies to the brain; however, its functions are ensured by an extremely complex interplay of different cell types and areas that are simultaneously recruited. Such complexity is extensively found in the human brain and is ensured by mechanisms of development that are not found in any other animal.

The cerebral cortex arises during embryonic life from two main categories of progenitors, radial glial cells (RGs) and intermediate progenitor cells (IPs) (48). Both progenitor types proliferate and differentiate in the process of corticogenesis. Two identical RGs are generated from replicative mitotic divisions of RGs, the stem cell reservoir of the cortex.

Differentiative divisions, instead, produce a new RG and either a newly born neuron or an IP. Unlike RGs, IPs are committed to giving rise to neurons exclusively and have a much lower proliferative potential, as they will self-replicate only two or three times. Although RGs and IPs are the two main progenitor types of the cortex in a variety of species, in higher-order animals, including humans, RGs' proliferative potential largely exceeds that of other animals. Consequently, the size of the cerebral cortex of higher-order animals is expanded and therefore folded to accommodate its expansion, thus differing from other (lower order) animals, where it is smooth (lissencephalic). As a consequence, areas assigned to different functions are more likely to be closer in proximity in folded brains, which may favor their connectivity (62). However, whether and how this may contribute to higher cognitive functions is difficult to determine.

Considering that upper cortical layers are the last to be established during corticogenesis, the largest differences in size and cell type heterogeneity are mostly detected in human upper cortical layers. It is, in fact, in these layers that most of the differences in human progenitors' proliferation will eventually accumulate (60). Importantly, many of the human-specific functions are exerted by upper cortical layers. Upper cortical layers are implicated in cortico-cortical connectivity (63), which contributes to integrated processing of sensory input, memory, abstract thought, and, in frontal cortical regions, higher-order cognitive functions. Large-scale MRI "brain charts" are able to quantify how these developmental programs diverge across primates. In humans, cortical gray matter volume continues to expand until middle childhood (~6 yr), whereas the total surface area peaks only in late childhood to early adolescence. White matter growth, on the other hand, stretches well into the third decade. Rhesus macaques, in contrast, reach peak gray matter volume at ~9 mo, with cortical thickness and surface area plateauing within the first postnatal year. As a result, they are born with more than 50% of their adult brain size, whereas human life starts with barely 25%–30%. This prolonged human expansion lengthens the window during which activity-dependent processes can sculpt association circuits and may underlie our exceptional cognitive plasticity (64, 65).

In recent years, our understanding of the molecular specialization of mechanisms underpinning human brain development has grown exponentially. Specifically, the discovery of human-specific gene sets expressed solely in the developing human brain has helped to elucidate the molecular basis of human-specific features, such as increased brain volume being attributed to an extended period of cell division and the increased complexity in short and long connectivity within the cortex and with subcortical brain areas (66). Furthermore, human-specific mechanisms of corticogenesis drive cortical progenitors to produce not only glutamatergic projection neurons but also GABAergic inhibitory interneurons (67). This may contribute to enhanced cognitive abilities by supporting a finely tuned balance between excitation (facilitating integration) and inhibition (providing modulation). Notably, the overall ratio of excitatory to inhibitory neurons in the cortex is 4:1 (68, 69), although this can vary between species and cortical regions. For example, higher-order associative areas, such as the prefrontal cortex, may contain a relatively higher proportion of inhibitory interneurons, potentially reflecting the greater demand for information gating and cognitive control in humans compared with rodents (70).

Overall, specialized developmental processes specific to human brain development contribute to the production of the anatomical substrate on which the human brain's functions will rely in adulthood. Yet, our description of the mechanisms through which such substrate is created is far from being complete. Nevertheless, there has been much effort to identify cellular properties and subtypes that are exclusively found in humans, which substantially contribute to the uniqueness of our brains.

Human Neuron Morphology and Specialization

During evolution, the adult human cortex has expanded not only in surface area but also in its layer thickness. Layers 2 and 3 (L2/L3) have increased disproportionally compared with other mammalian species (71, 72). Supragranular layer thickness is largest in humans (~50%) and other primates (46%), followed by carnivores (36%), and then rodents (19%), suggesting a distinct difference in the proportion of cortex devoted to corticocortical connectivity (71). With cortical expansion, properties of cortical cells have also changed: the human cortex contains more cells (73), many of these cells are larger, with larger protrusions covering more area (Fig. 1) (49, 74–77). As neurons increase in size, they require more space for larger dendrites and axons, and this process goes hand-in-hand with a decrease in neuronal densities. In the human cortex, neuronal size increases from upper L2 to deep L3 neurons, whereas the neuronal density decreases (37, 78). In addition, thicker cortical layers L2/L3 in different cortical areas and subjects generally contain larger neurons at lower densities (37). This holds for pyramidal neurons, interneurons and astrocytes in the human cortex (37, 75–77, 79, 80). The larger human pyramidal neurons carry more dendritic spines that are larger, longer, and more densely distributed along the dendrite (81, 82). Human pyramidal neurons receive more synapses than in other species (83), particularly in L2/L3, suggesting that they integrate more synaptic information (84).

Both neuronal and glial cells, which outnumber neurons 2:1 in human neocortex (70, 85), show specialized physiological properties. The human cortex contains several types of astrocytes, some of which are projecting protrusions to other layers, which is not the case in the rodent cortex. Human astrocytes are 10 times larger and more complex than their rodent counterparts, calcium waves generated in astrocytes are more pronounced, have faster rise time kinetics, and propagate five times faster (76). Several primate-specialized, and even human-specialized, interneuron types have been described, each with morphological and physiological adaptations not found in rodents (75, 79, 83, 86, 87). Ramon y Cajal identified the double-bouquet interneuron with its characteristic horsetail axons that are prominent in primate cortex, generating structural "microcolumns," but whose function is still elusive (75, 88). Human and macaque cortices contain Somatostatin (SST)-positive interneurons with intrinsic persistent activity that could be triggered by single action potentials (APs) and which was associated with a depolarizing plateau potential induced by the activation of persistent Na^+ currents (87). In layer 1, the human-specialized Rosehip interneuron was identified that predominantly

targets apical dendritic shafts of layer 3 pyramidal neurons and inhibits backpropagating pyramidal action potentials in microdomains of the dendritic tuft, potentially controlling of distal dendritic computation in cortical pyramidal neurons (79, 86). These specialized interneuron types may provide the human cortex with specific microcircuit elements relevant for human brain function. But not only does the human central nervous system harbor unique cellular subtypes, it also displays very specific properties in terms of connectivity, conductivity, and network dynamics. Mesoscale functional brain dynamics underscore the unique systems-level context in which specialized human neurons operate. Dynamic coactivation modes from resting-state fMRI scans in awake mice, macaques, and humans demonstrate a conserved repertoire of brain-wide states. However, humans dwell disproportionately longer in an integrative, default-like state that bridges sensorimotor and transmodal cortices, whereas macaques and mice favor a segregated sensory state (89).

Neuronal Connectivity and Electrophysiological Properties of the Human Brain

In contrast to rodent L2/L3 pyramidal neurons, human pyramidal neurons robustly express hyperpolarization-activated cyclic nucleotide-gated (HCN1) channels in soma and dendrites (90). Activation of dendritic I_h currents can facilitate the transfer of synaptic inputs received on distal dendrites to the soma. Changes in HCN properties, such as phosphorylation signaling, can contribute to human epileptogenesis (91). Increased neuronal size in general may result in other compensatory mechanisms that ensure fast and efficient information transfer. Large dendrites impose a substantial impedance load onto the axon initial segment, resulting in faster action potential (AP) onset and, consequently, increased capability of timing action potential firing relative to high-frequency inputs (92). Rapid AP initiation properties facilitate information processing by neurons (93). Fast AP onset kinetics allows human pyramidal neurons to time action potential firing to synaptic inputs at considerably higher frequencies, with reliable input-to-output conversion of subthreshold membrane potential frequencies up to 1,000 Hz, five times faster than rodent pyramidal neurons (94). Properties of voltage-gated sodium channels in human pyramidal neurons support fast AP onset kinetics and stability, with shifted voltage dependence, and reduced inactivation properties (95). Fast AP onset kinetics in human pyramidal neurons are also more stable during high-frequency action potential firing, suggesting that human neurons maintain fast processing properties when neurons are engaged in cognitive tasks (96–98). Fast action potential kinetics are linked to human cognitive ability. L2/L3 pyramidal neurons from individuals with higher IQ scores are much more able to maintain fast action potential kinetics during persistent firing than in individuals with lower IQ scores, supporting the importance of fast signaling for human cognition (37, 99).

Action potentials in human L2/L3 pyramidal neurons not only have faster kinetics but also have a prominent afterdepolarization, distinguishing them from those in rodents (94, 100). This afterdepolarization reflects active dendritic properties and depends on the activation of dendritic L-type voltage-gated Ca^{2+} channels. These dendritic properties set the rules for spike timing-dependent synaptic plasticity (STDP) in human neurons, which are different from rodent STDP rules: human pyramidal neurons associate inputs arriving during larger temporal windows (94, 100). Dendrites of L2/L3 pyramidal neurons are more excitable than those in rodents, and this increased excitability is mediated by dendritic calcium action potentials (dCaAPs) (101). In contrast to typical all-or-nothing APs, human dendritic CaAPs are graded, with maximal amplitude at threshold stimuli, but tapering off for stronger stimuli (101). They might therefore act as an anticoincidence detector, enabling human pyramidal neurons to perform the exclusive-or (XOR) operations, previously thought to require multiple neurons, and contributing to nonlinear dendritic computations of single pyramidal neurons acting as a multilayer network (102).

In contrast, human L5 pyramidal neurons fall into distinct types based on their transcriptome that differ in dendritic excitability. Extratelencephalic (ET) projecting L5 pyramidal neurons express HCN channels and have electrogenic dendrites firing all-or-nothing dendritic action potentials, like rodent L5 pyramidal neurons (103). In contrast, intratelencephalic (IT) projecting L5 pyramidal neuron dendrites were much less excitable. In studies that did not distinguish L5 human pyramidal neurons based on transcriptomics, these neurons were reported to have reduced dendritic excitability compared with rodents and eight other species (104, 105). In nonhuman species, conductance densities of voltage-gated potassium and HCN channels in layer 5 cortical pyramidal neurons seem to follow conserved allometric rules (105). Species with larger neurons had higher membrane conductance, with a conserved conductance per unit brain volume. Human L5 pyramidal neurons did not obey this allometric relationship, exhibiting much lower voltage-gated potassium and HCN conductance (105).This results in a larger compartmentalization of human L5 pyramidal neuron dendrites, creating more independently acting computational units (104, 106). At present, it is not settled whether this holds only for IT-projecting L5 pyramidal neurons in human cortex or also for ET-projecting pyramidal neurons.

Synaptic connectivity in the human cortex also shows several substantial adaptations compared with rodents and other species. In addition to triggering monosynaptic postsynaptic responses, single action potentials of human L2/L3 pyramidal neurons can trigger complex events, i.e., long-lasting sequences of events in the cortical network consisting of alternating glutamatergic and GABAergic postsynaptic potentials (107). These complex events rely on particularly strong excitatory synapses terminating on fast spiking interneurons (108), which contain five times more vesicle release sites than rodent excitatory presynaptic terminals (109). Excitatory synapses formed between L2/L3 pyramidal neurons are also larger in strength and reliability than in rodent cortex (110). Although rodent glutamatergic synapses fail to release every fourth presynaptic action potential (25% failure rate), human glutamatergic synapses do not fail; every action potential results in glutamate release (110). Moreover, human glutamatergic synapses recover four times faster from depression (94), which considerably shortens the time window of loss of information transfer of the synapse in the depressed state during repeated action potential firing. Thereby, synaptic signal propagation in human cortical networks is substantially more efficient. As a matter of fact, several adaptations in feedforward and lateral

inhibition circuitries in human cortex ensure fast signaling and synchronization of activity, despite larger neuron-to-neuron distances and larger neuronal dimensions (77). The large glutamatergic synapses on fast spiking interneurons enable them to rapidly fire an action potential in response to single pyramidal neuron action potentials with short delay (108). Larger dendrite diameters and HCN channel expression in both human pyramidal neurons and fast spiking interneurons facilitate rapid signal propagation within neuronal dendrites for fast input-output processing (90, 92, 95, 111). The synaptic delay of inhibitory transmission between fast spiking interneurons and pyramidal neurons is shorter in human cortex than in rodent cortex (77). Together, these adaptations enable short delays in lateral and feedforward inhibition of human pyramidal neurons through fast spiking interneurons.

As in the rodent cortex, synaptic properties in human cortex are cell-specific (112, 113). Although excitatory synapses on parvalbumin-positive interneurons are depressing, excitatory synapses onto human somatostatin-positive interneurons are facilitating (77, 113, 114). Human pyramidal neuron networks do not show an overrepresentation of reciprocal connections, but network connectivity in human cortex exhibits a directed topology (115). Although connection probability decreased with increasing lateral distance and toward the apical dendrite, the connection probability between pyramidal neurons increased when the postsynaptic soma was located at deeper positions along the vertical axis (115). This could be a shared principle across species, as it was also found in the rodent cortex (116). Recent electron microscope-based connectomics studies of human neocortex reveal that connectivity between interneurons is strongly increased, resulting in a 10-fold expansion of interneuron-to-interneuron networks in human cortex (117). Moreover, some neurons made exceptionally powerful connections with neighboring neurons, consisting of more than seven contact points, ranging up to more than 50 contact points between two neurons (85). These powerful connections could be formed between excitatory and inhibitory neurons alike and occurred far more often than expected by chance (85). But the exact role of these powerful connections remains to be elucidated. Connectomics has just begun to address the human cortex, and adult human synaptic connectivity function has been addressed in very few studies, so many properties of human cortical circuitry remain unexplored and to be discovered. However, cross-species alignments of resting-state functional connectomes situate human and macaque brains along a common unimodal-to-transmodal axis. Homology is highest in primary visual and somatomotor territories but declines sharply toward association cortices, with the deepest gulf surrounding posterior default-mode, temporoparietal, and anterior-cingulate hubs, regions that also underwent the greatest areal expansion during primate evolution. Within individual sensory hierarchies, a similar pattern emerges: in the auditory system, nonprimary belt and parabelt fields vary more across humans and show stronger long-range coupling to associative networks than their macaque counterparts (118). Together, these observations suggest that human association networks are not simply scaled-up versions of those in other primates but have been functionally retuned, with default-mode hubs occupying the most recent tip of an ancestral sensorimotor-to-transmodal gradient.

Molecular Properties and Transcriptomic Signatures of the Human Brain

Another powerful tool to shed light on cellular identities and interspecies differences can be found in rising technologies, such as single-cell genomics and transcriptomics. Single-cell genomics have dramatically expanded our understanding of the human brain's cellular complexity, unveiling a wide variety of distinct cell types and states characterized by their unique gene expression profiles. Advances in this technology have led to the creation of a comprehensive atlas of more than 5,000 distinct cellular clusters in the mouse (25), whereas a draft human brain atlas described more than 3,000 transcriptomic cell types across a sampling of 100 brain regions (24). Studies of the human cortex have revealed that each cortical area comprises ~100 transcriptomically defined cell types (68, 119–121). Cytoarchitecturally distinct cortical areas can be defined by their unique proportional composition of cell types, with human primary visual cortex standing out as particularly distinct from other cortical areas in its cellular composition (121).

These studies have enabled comparative transcriptomic approaches that have facilitated direct comparisons of conserved cell types across humans, nonhuman primates (NHPs), and rodents (34, 68, 121–123). Such studies highlight a broadly conserved hierarchy of cell types across species while also revealing notable differences in cellular makeup and gene expression. For instance, in the primary motor cortex (M1), the ratio of glutamatergic to GABAergic neurons varied between species, with humans exhibiting a 2:1 ratio, marmosets exhibiting a 3:1 ratio, and mice exhibiting a 5:1 ratio (34). Interestingly, the proportions of GABAergic subclasses and cell types were similar across species in M1, suggesting a global increase in GABAergic types in humans compared with marmosets and mice rather than a specific increase in certain subclasses. A recent study comparing cellular diversity and gene expression in the middle temporal gyrus (MTG) demonstrated striking similarities in cellular architecture across humans, other great apes (chimpanzees and gorillas), macaques, and marmosets (121). Notably, humans and other great apes shared nearly identical proportions and laminar distributions of conserved cell types. However, many differences in gene expression were found across species. For example, although cell subclasses had a similar number of marker genes across species, only 10%–20% of these genes showed strong conservation of expression specificity. Notably, chimpanzee neuronal subclasses were found to be more similar to gorilla than to human, despite chimpanzees sharing a more recent common ancestor with humans, suggesting that neurons in the human lineage have changed more rapidly since the evolutionary divergence of humans from chimpanzees. Interestingly, glial cells, apart from oligodendrocyte precursor cells (OPCs), exhibited greater expression changes between species compared with neurons. Expression changes were more pronounced in oligodendrocytes, astrocytes, and microglia than in neurons. Human astrocytes showed increased expression of genes involved in synaptic signaling and protein translation, such as *SPARC* (osteonectin) and *SPARCL1* (hevin). Expression differences in extracellular matrix (ECM)-related proteins like brevican, neurocan, and phosphacan were also

apparent in human astrocytes compared with nonhuman primates. Furthermore, human-specific transcriptional differences were marked by substantial alterations in isoform usage, even in genes with conserved expression levels across species. Genes exhibiting human-specific switches in isoform usage included genes involved in axon guidance and chromatin remodeling that may contribute to the molecular and functional specializations of the human brain (121).

VALIDATION OF PRECLINICAL STUDIES

In the last decades, basic research and preclinical studies have focused on identifying novel and improved treatment options for human diseases (124). Preclinical studies traditionally rely on cell culture systems or animal models and aim to unravel the mechanisms of pathology to identify new therapeutic targets that may lead to advanced treatments in humans (125). However, as previously mentioned, translational failures occur frequently (126–129). To validate preclinical studies, expensive and elaborate clinical trials in patients are required, often costing millions of dollars per trial. In particular, clinical phase 3 trials carry a high risk of failure (1, 125, 130, 131). This risk is especially pronounced in CNS-related drugs compared with non-CNS-related drugs, with nearly half of CNS drug trial failures attributed to a lack of efficacy in patients (Fig. 2) (1).

The limited success in translating findings from cell culture, rodent, and other animal models into effective treatments for human neurological diseases underscores the urgent need to examine the functional properties of the human brain at the resolution of specific cell types and neuronal circuits (132). Although animal and in vitro models have provided invaluable insights into fundamental neurobiological mechanisms, their predictive validity for human clinical outcomes remains limited due to species-specific differences in brain architecture, gene expression, and circuit organization. Consequently, there is a critical need for complementary approaches that leverage human brain tissue to model neurological diseases such as epilepsy, neurodegenerative diseases, and brain tumors. Although challenges such as tissue availability and heterogeneity persist, these human-based models offer more relevant platforms to evaluate drug efficacy, identify novel therapeutic targets, and understand disease-specific pathophysiology within the native cellular and circuit context. Integrating human tissue models with traditional preclinical systems represents a promising strategy to improve translational success and accelerate the development of effective treatments.

In *Human-Specific Experimental Platforms*, we will review the opportunities and limitations to study these questions in acute human brain slices, human organotypic slice cultures, and human organoids to overcome the problems of translation to the human brain (Fig. 3).

Human-Specific Experimental Platforms

Human brain tissue and derived models provide invaluable tools for validating findings from animal models in a human-specific system before progressing to clinical studies. Two primary approaches include the use of human acute or organotypic brain slices and three-dimensional cerebral organoids. These models enable the study of human brain physiology, pathology, and drug responses, offering complementary platforms for preclinical research.

Human brain tissue can be obtained from neurosurgical cases, such as tumor and epilepsy resections (Fig. 3*A*). These slices, either of pathological origin or as healthy access tissue, can be used directly for various experimental applications (133, 134). Culturing human organotypic brain slices enables long-term observation and manipulation, such as the introduction of reporters, gene-modulatory elements, or molecular tools via viral transduction (135–139) (Fig. 3*B*).

In contrast, human cerebral organoids are three-dimensional cultures of pluripotent stem cells differentiated into neural tissue that mimic the human brain (140, 141). Organoids recapitulate features of in vivo cell growth, allowing self-organization, differentiation, and heterogeneity within the culture environment (140, 141). They have been used to study a variety of neurological and developmental conditions, including microcephaly (139), Alzheimer's disease (142, 143), Parkinson's disease (144), amyotrophic lateral sclerosis (ALS) (145), tuberous sclerosis (146), autism (147), and Rett syndrome (148). Recent advancements have increased organoid complexity to include microglia (149, 150) and vasculature (151). However, important limitations remain, such as incomplete maturation,

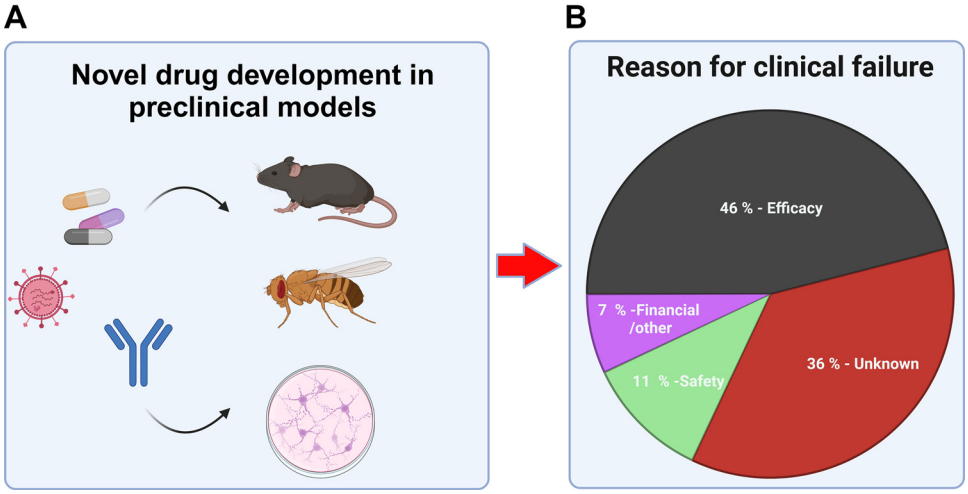

Figure 2. From preclinical studies to novel treatments. *A*: many promising novel therapy options arise from preclinical model systems. *B*: 46% of phase 3 clinical trials failed to prove efficiency in humans. Data adapted from Kesselheim et al. (1) (from the 132 initiated phase 3 studies, 70 were discontinued for the depicted reasons). Figure, in part, created with a licensed version of BioRender.com.

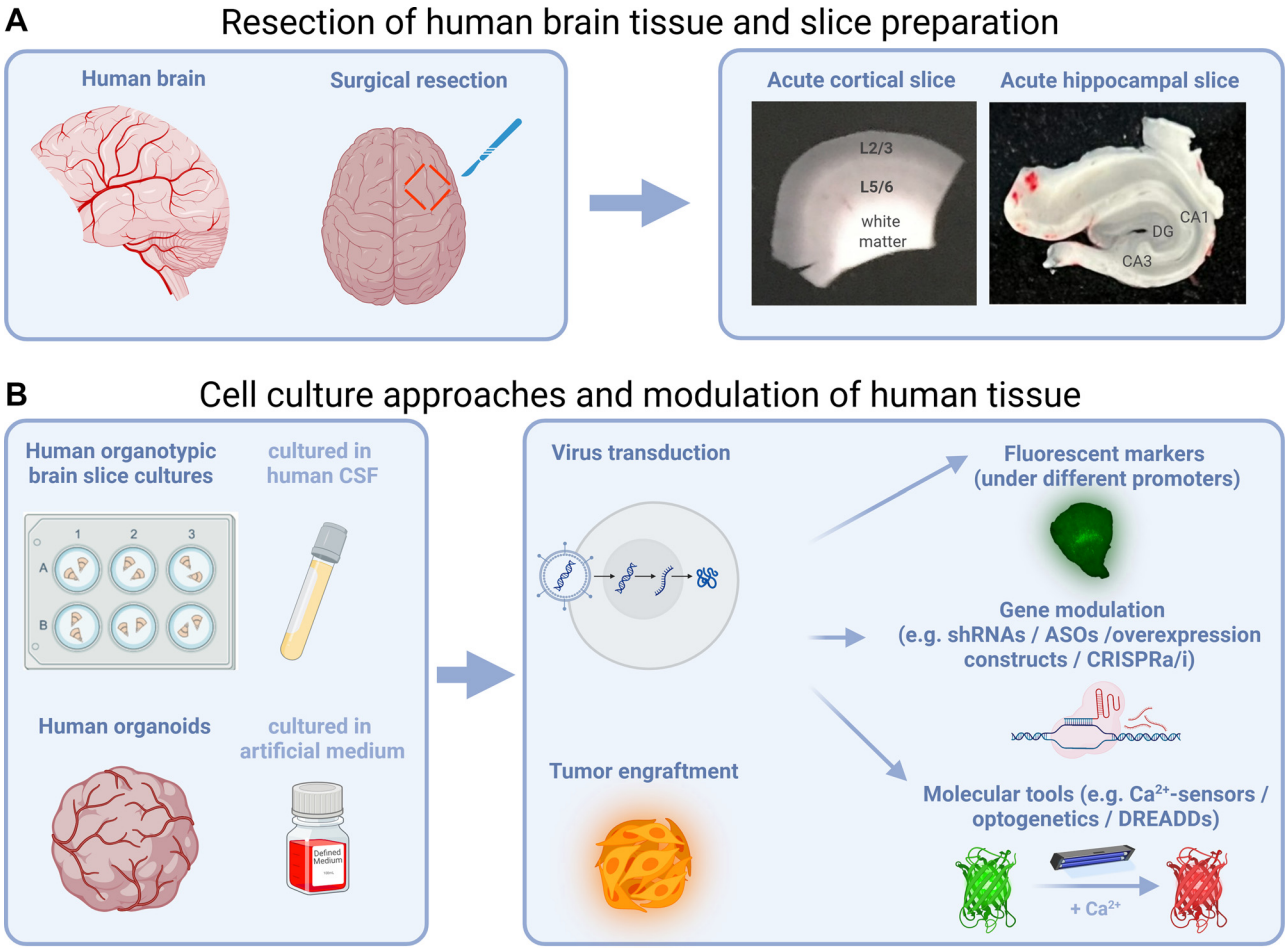

Figure 3. Toolbox to study research questions using surgically resected human brain tissue. *A*: access tissue or tissue with underlying pathology can be used for experiments in acute slice preparations. *B*: human organotypic brain slice cultures and human organoids allow targeted investigations such as viral labeling of specific cells, gene modulation, and induction of pathology. Figure, in part, created with a licensed version of BioRender.com.

limited cellular diversity, reduced synaptic connectivity compared with in vivo tissue, and challenges in recapitulating long-term disease progression and brain-wide network interactions, which currently restrict their ability to fully model human brain physiology and pathology (152, 153).

Standardization of methods and analytical techniques across laboratories is critical for maximizing the utility of these human-specific models. Significant progress has already been made in defining neuronal cell types through transcriptomic, morphological, and electrophysiological analyses. These efforts facilitate direct comparisons of preclinical data obtained from human brain tissue across different research groups (68, 154, 155). Moreover, such standardization could include the collection and shared analysis of tissue banks that provide data from distinct and rare pathologies.

These human-specific systems, whether based on slices or organoids, can be applied to a multitude of experimental applications, including electrophysiological recordings, transcriptomics, histology, and imaging (Fig. 4). Recent advancements have expanded this toolbox to include two-photon microscopy, which enables high-resolution imaging of neuronal morphology and activity in intact tissue, and multipatch electrophysiology, which allows simultaneous recordings from multiple neurons to assess local synaptic connectivity and microcircuit dynamics (115, 156, 157). Moreover, multiomics approaches, such as single-cell and single-nucleus RNA sequencing, proteomics, and metabolomics, are increasingly used to dissect the molecular and cellular complexity of human brain tissue in both health and disease (158–161). Combining in vivo measurements from patients with subsequent ex vivo recordings and analyses of tissue samples from the same individuals holds great promise for identifying novel biomarkers and therapeutic targets (132). These approaches not only help to resolve interindividual variability but also facilitate the development of personalized strategies for diagnostics and therapy. Furthermore, they can be adapted to model specific diseases and investigate pathogenesis, disease progression, and potential therapeutic targets or compounds (162–164). In the following section, we will elaborate on how disease can be modeled in human tissue, focusing on epilepsy and glioblastoma (GBM).

Human Model Systems to Study Epilepsy

Despite the development of many new drugs, treatment with antiseizure medications (ASMs) has not resulted in a significant improvement in therapeutic outcomes. Although ASMs achieve seizure freedom in ~60% of treated patients (2), they generally reduce excitability in all neurons, leading

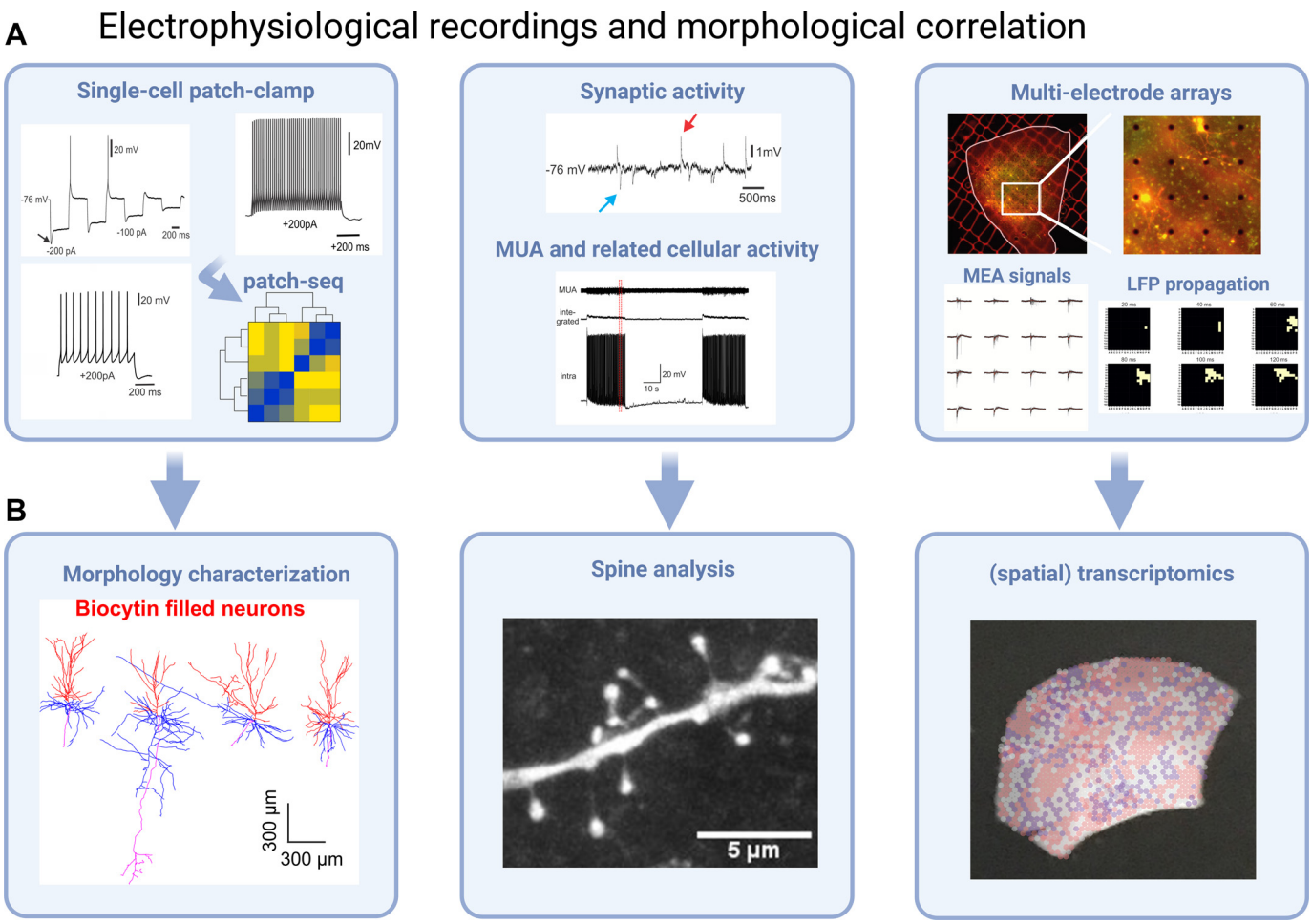

Figure 4. Experimental readouts in human tissue samples. *A*: electrophysiological recordings using whole cell patch-clamp recordings and measurement of active and passive properties of the neurons, synaptic and synchronous multiunit activity (MUA), cellular activity, and spatial-temporal network assessment using multielectrode array (MEA) recordings. *B*: morphological analysis of neurons and dendritic spines, as well as spatial transcriptomics, complement the electrophysiological measurements. Parts of the figure were adapted from Refs. 138 and 140 used with permission under CC-BY license. Figure, in part, created with a licensed version of BioRender.com.

to a range of side effects, including drowsiness, irritability, mood changes, weight gain or loss, dizziness, sleep disturbances, nausea, blurred vision, hair loss or unwanted hair growth, swollen gums, and shaking hands (165). Therefore, alternative and more precise treatment options and significant advancements in epilepsy research are urgently needed.

Numerous mechanisms underlying the development of epilepsy have been identified, ranging from genetic variants to immune-related processes and disturbances in brain development to traumatic brain injury. Initially, the investigation of acute brain slices of epilepsy patients after resective epilepsy surgery was successfully used to identify and further investigate cellular and molecular mechanisms that participate in ictogenesis (166–170). However, to what extent the activity in the slices might be in part physiological in nature is not entirely clear and is still under debate (170). Most likely, the same circuits that underlie seizure generation are also part of physiological behavior, such as slow-wave sleep and memory formation (171, 172). Although studies in acute slices are essential to understand the basic principles of the human brain, novel protocols that allow stable human organotypic slice cultures with intact cellular and network function open novel experimental paradigms that are not possible in the acute preparations (135, 138, 164, 173).

Gene therapy using adeno-associated viruses (AAVs), heralded for its cell-specific precision, has shown promising effects in rodent models of epilepsy (174). However, our understanding of pathological hyperexcitability in the human brain and the potential for cell-specific modulatory techniques remains limited. The primary goal is to genetically target and modify the activity of specific subsets of cells in the human brain. In recent years, several successful attempts have been reported in achieving highly specific, viral vector-mediated expression in selected cell types in nonhuman primates (175) and human slice cultures (75, 173, 176, 177). This approach offers the potential to target cells within epileptic foci using novel genetic strategies to minimize side effects and optimize therapy. For instance, the overexpression of genes to reduce seizure activity has been validated in preclinical studies using animal models (178–181) and was, in parts, validated in human organoids (180).

Furthermore, viral delivery of genetic tools may enable advanced, on-demand activation or inhibition of cells through

optogenetics (opsins) (182–184) or chemogenetics (185). Several of these tools have already been tested in human organotypic slice cultures and proven to be functional (177, 186). However, further refining the recording electrodes and coupling these tools to closed-loop systems for in vivo use remain a significant technical challenge that must be addressed before they can be applied in clinical settings (187, 188).

Human Model Systems to Study Glioblastoma

Glioblastoma (GBM) is the most common primary brain cancer, with a dismal prognosis. Despite maximal surgical resection, chemotherapy, and radiation, recurrence and mortality are inevitable. GBM is shaped by developmental programs, genetic drivers, and, importantly, the tumor microenvironment (TME) (189–193). Recent work has shed light on the importance of interactions of glioma cells with the normal brain's neurons, glia, and immune cells (191, 194–196). Although several novel therapies, such as immunotherapies, angiogenesis inhibitors, and alternative drug delivery methods, have been explored (197–199), these approaches have failed to significantly extend overall survival, highlighting a critical translational gap between preclinical research and clinical efficacy (200).

One of the main issues lies in the use of animal models, such as genetically modified rodents or xenografts, which do not fully replicate the complex tumor microenvironment, cellular heterogeneity, and immune landscape of human GBMs (201, 202), leading to species mismatch (203). Although these models have been valuable for understanding tumor biology and testing treatments, they lack the ability to accurately mimic human GBM pathogenesis, progression, and therapy resistance (204, 205). For instance, rodent models often fail to reproduce the dynamics of blood-brain barrier (BBB), which play a crucial role in therapeutic delivery (206, 207). Moreover, the discrepancy in immune system responses and CNS-specific interactions between animal models and humans presents challenges in translating promising preclinical results to clinical settings. The failure to consider these factors results in a significant gap in translating new therapies from bench to bedside. Thus, there is a need for more advanced and representative models that better mimic human GBM, such as organotypic brain slice cultures, which have shown promise in more closely modeling tumor growth, immune environment, and therapeutic responses observed in humans (205, 208, 209).

Organoid technology also holds promise for GBM research. Although only ~5% of traditional GBM culture models can be correctly classified as brain tumors, all tested GBM organoid models can be transcriptionally classified as GBM with high confidence (210). Organoids may overcome the limitations of traditional 2-D and tumor sphere cultures by maintaining cellular diversity seen in patient tumors and modeling the TME and its microenvironmental gradients (211–213). Human GBM cancer stem cells have been cocultured with human cerebral organoids, allowing for interactions between cancer and noncancer cells without species mismatch (212, 214). Indeed, such cocultured organoids form microtubule transport networks mimicking GBM invasion (212). Single-cell RNA sequencing of GBM organoids shows that an appropriate diversity of cell types is recreated compared with sets of patient-derived GBM tissue and glioma spheres (215) Furthermore, recent evidence has demonstrated the ability of GBM tissue to transfer mRNA to nonmalignant organoid cells through an extracellular vesicle-mediated process (216). By using the patient's own tumor tissue in a cerebral organoid, it is possible to take advantage of patient-specific genetic information and construct a personalized precision medicine platform for drug screening.

CONCLUSIONS AND OUTLOOK

Over millions of years, the human brain has evolved distinct features, particularly within the neocortex, resulting in increased size, complexity, and unique cellular composition due to specialized molecular expressions and intricate connectivity. Human neurons are notably larger with extensive dendritic branches, enhancing synaptic connections and information processing capabilities. These structural and functional specializations give rise to the ability to engage in abstract thinking, express empathy, use complex language, and create sophisticated tools.

Recent single-cell genomic studies have uncovered a diverse array of brain cell types, further highlighting the functional specialization of the human brain. Moreover, glial cells have emerged as active contributors to neuronal function, influencing synaptic activity and neural circuitry beyond their traditional supportive roles. Despite these advances, the full extent of cellular functional specialization and its implications for cognition and disease remain areas to be explored.

Future research should focus on further elucidating how specific cellular properties contribute to higher cognitive functions and exploring their roles in neurological disorders. Using integrative approaches that combine genomics, transcriptomics, electrophysiology, and advanced imaging in human tissue samples will be crucial. Comparative studies across species will enable us to investigate evolutionary developments leading to our unique cognitive abilities. Importantly, bridging the translational gap through the development of human-specific disease models holds promise for transforming these insights into clinical applications. Continued research into the human brain's complexities will deepen our understanding of its unparalleled capabilities and inform strategies to address its vulnerabilities.

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AUTHOR CONTRIBUTIONS

K.M.J.v.L., A.B., R.H., F.B., J.S.B.R., S.N.E., A.H., H.D.M., N.A.G., and J.-M.R. prepared figures; K.M.J.v.L., A.B., R.H., F.B., J.S.B.R., S.N.E., A.H., H.D.M., N.A.G., J.-M.R., and H.K. drafted manuscript; K.M.J.v.L., A.B., R.H., F.B., J.S.B.R., S.N.E., A.H., H.D.M., N.A.G., J.-M.R., and H.K. edited and revised manuscript; K.M.J.v.L., A.B., R.H., F.B., J.S.B.R., S.N.E., A.H., H.D.M., N.A.G., J.-M.R., and H.K. approved final version of manuscript.

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