REVIEW

The emergent properties of the connected brain

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There is more to brain connections than the mere transfer of signals between brain regions. Behavior and cognition emerge through cortical area interaction. This requires integration between local and distant areas orchestrated by densely connected networks. Brain connections determine the brain's functional organization. The imaging of connections in the living brain has provided an opportunity to identify the driving factors behind the neurobiology of cognition. Connectivity differences between species and among humans have furthered the understanding of brain evolution and of diverging cognitive profiles. Brain pathologies amplify this variability through disconnections and, consequently, the disintegration of cognitive functions. The prediction of long-term symptoms is now preferentially based on brain disconnections. This paradigm shift will reshape our brain maps and challenge current brain models.

New ideas often emerge through close interaction between minds. Accordingly, these ideas do not solely belong to any of these individual minds but rather are the fruit of their integration—an emergent property of mutual exchange and interaction. The concept behind integration comes from emergentism, which postulates that "the whole is something besides the parts" (*1*) and that "no complex system can be understood except through careful analysis; however, the interactions of the components must be considered as much as the properties of the isolated components" (*2*). In neuroscience, there is a growing consensus that functions are an emerging property of the interaction between brain areas (*3*). Thus, function-specific brain activity involves the integrative effort of several brain regions (*4*). White matter connections support this integration by interconnecting brain regions (Fig. 1). With cortical expansion, these connections have evolved to preserve interactions between distant regions (*5*). These connections support local, intra- and interlobar associations, projection, and interhemispheric commissural circuits (*6*). These circuits create networks by stringing together many brain regions to orchestrate a brain symphony conducted by finely attuned connections with variable caliber and myelination tailored to their functional role (*7*).

Measuring brain connectivity in the living brain

Today, the connections between brain regions are noninvasively measured in the living human brain using neuroimaging methods that unveil their structure (i.e., axon bundles) and their function (i.e., synchronization of regional activity). Structurally, diffusion-weighted imaging (DWI) measures water diffusion along the directions of axons and can derive properties such as trajectory (i.e., tractography), density, caliber, and dispersion (*8*). Functionally, the communication between brain regions can be extrapolated by measuring the coherence between distant areas' activity, mainly through functional magnetic resonance imaging (fMRI). Mathematical models applied to fMRI can estimate communication strength (i.e., functional connectivity) or directionality (i.e., effective connectivity) (*9*). Because regions that fire together wire together (*10*), measuring communication between regions indicates their connections, albeit these regions are not always directly connected (*11*).

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The integrative functional role of brain connectivity

There is, however, more to brain connections than the mere transfer of signals between brain regions. Connections can amplify or reduce brain signals (*11*) and determine the brain's cortical structure and function. Specifically, there is a similarity between the synchronized communication between brain regions at rest and their activity during tasks at the group (*12*) and the individual (*13*) levels (Fig. 2A). It is also possible to predict where a function will arise in the developing brain on the basis of the cortical projections of white matter tracts alone. For instance, the latter has been demonstrated for identifying the visual word form area, even before the acquisition of literacy (*14*). Typically, the main trends of brain connectivity capture the spatial organization of functions in the brain (*15*). Deprived of its connections, a brain region will prune its remaining dendrites and synapses, and its neurons will wither or die (*16*). Consequently, this region's network breaks down functionally [i.e., dysconnection (*17*)] and structurally (i.e., disconnection) and no longer can contribute to a function. This phenomenon, also known as diaschisis (*18*), demonstrates the critical importance of connections in maintaining the integrity of distant brain regions and their functioning. Lastly, animal studies that surgically swap connections between sensory cortices have further demonstrated the leading and decisive role of white matter connections within the brain's functional organization. Specifically, forcing visual inputs onto the auditory cortex alters it to acquire many of the cytoarchitectonic and functional properties of the visual cortex (*19*) that are associated with normal visual behavior (*20*). This indicates that cell properties are mediated by their connections through their interaction with the rest of the brain, and moreover, those brain functions are an emerging property of these integrative mechanisms. Thus, as previously hypothesized (*21*), this sum of evidence demonstrates that brain connections support the latent mechanisms that determine the function of the brain and cognition as we know it.

This shift away from considering isolated regions in favor of an integrated anatomical-functional network led to the reevaluation of functional activations with regard to their white matter connections. Accordingly, brain connections revealed by the highest-resolution tractography (*22*) can be used to systematically decipher human activation networks and recently led to the first functional white matter atlas (*23*). This atlas identifies the joint contribution—or integration—of structurally connected brain areas by a statistical association of fMRI and diffusion data (Fig. 2B). The result also revealed a leftward asymmetry between the known granularity (i.e., the level of detail) of functions of the left and the right hemispheres. This asymmetry reflects an epistemological imbalance (i.e., we know more about the cognition of the left than the right hemisphere), leading to a publication bias and triggering the necessity for more dedicated cognitive explorations of the right hemisphere, which for a long time was considered the minor or nondominant hemisphere.

The mechanisms that sustain the lateralization of brain functions are related to interhemispheric connections. Some cortical regions show increased functional asymmetries for cognitive functions such as language, perception and

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action, emotion, and decision-making. These cortical regions are less connected with the contralateral hemisphere via the corpus callosum (Fig. 2C) (*24*). DWI has revealed that the structure of the corpus callosum changes along with brain size across and within species (*25*, *26*). In particular, the axonal conductive properties can change (*27*), and axon calibers correlate with the interhemispheric speed of conduction (Fig. 2D) (*28*). Further, a trade-off in the number of connections exists between interhemispheric and intrahemispheric connectivity across species (*25*). Taken together, these studies suggest that during evolution, brain size expansion may have led to functional lateralization to avoid a disproportionate corpus callosum or excessive conduction delays across hemispheres.

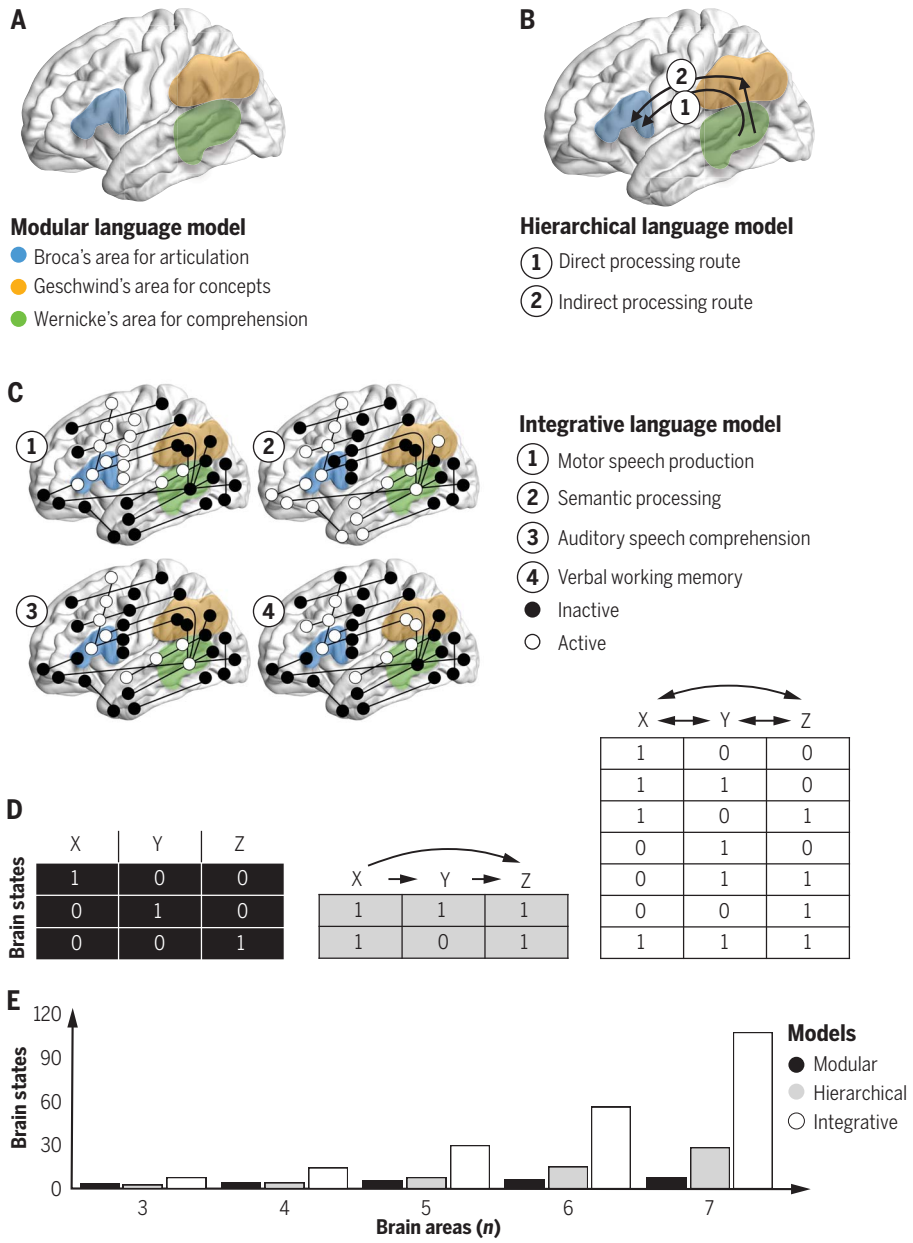

Fig. 1. The superior flexibility of the integrative brain model compared with other classical models, as exemplified by simplified language models. Brain models determine the flexibility of brain states (i.e., functions). In a modular system (**A**), one region performs one function without cross-talk, and the number of possible brain states increases linearly with the number of regions. In the hierarchical system (**B**), functions emerge from the sequential activation of regions. Accordingly, the repetition of words or sentences would rely on the temporal-parietal-frontal propagation from auditory-to-motor processes. In contrast to (A) and (B), the integrative model (**C**) offers the highest computational flexibility, allowing for the high complexity and flexibility of language processes as we know them. Each model can be translated into different brain state patterns (**D**) across brain areas X, Y, and Z. Each line indicates a brain state (function) (courtesy of Chris Foulon). (**E**) Illustration of the interaction between the brain model and the number of areas involved in the number of brain states a system can take.

Mapping evolution through connectivity

As structural connectivity can be used to decipher the brain's functional organization, multiple studies compared different primate species to understand human uniqueness and shed light on the mechanisms involved in its evolution. For instance, human language capacity parallels the extraordinary expansion of the arcuate fasciculus in the left hemisphere (Fig. 3A) (*29*). The anatomical delineation of white matter tracts (e.g., arcuate fasciculus or corpus callosum) allowed for extracting corresponding connectivity profiles across species. This point of comparison permitted the computation of deformation fields between species' brains (Fig. 3B) (*30*). These deformation fields define similarities and differences across species. Comparative studies assume that similarities between species can be traced back to a common ancestor and account for the preservation of specific functions across evolution. Recent comparative work revealed one of the first comprehensive maps of the phylogenetic organization of brain regions (*30*). Such technical advances in comparative neuroimaging will allow for targeted studies that better match human brain mechanisms to their phylogenetic counterparts. These advances may also help discover and mimic neuroprotective mechanisms in animals that could potentially translate to improving human disease models and therapeutics. For instance, frontoparietal disconnection is a very sensitive (85%) and specific (95%) biomarker for persistent disorders of visual neglect (*31*). Whereas most humans with this disconnection will fail to recover from visual neglect, monkeys with the same disconnection will recover within a few days (*32*). Hence, there is a distinctive mechanism in monkeys that facilitates brain recovery. However, this mechanism has yet to be identified, and its translatability to humans needs to be explored.

One frequent limitation of comparative studies is the small number of brains per species used (usually fewer than 10), which fails to fully capture interindividual variability. While the amount of connectivity variability (i.e., magnitude) is proportional to the brain size, its pattern of variability is similar between humans and other primates. Accordingly, brain areas that have recently evolved increasingly differ between individuals, whereas evolutionarily older areas tend to be more stable (*33*). Intraspecies variability in brain connections might therefore be a novel dimension to our understanding of evolutionary mechanisms (Fig. 3C).

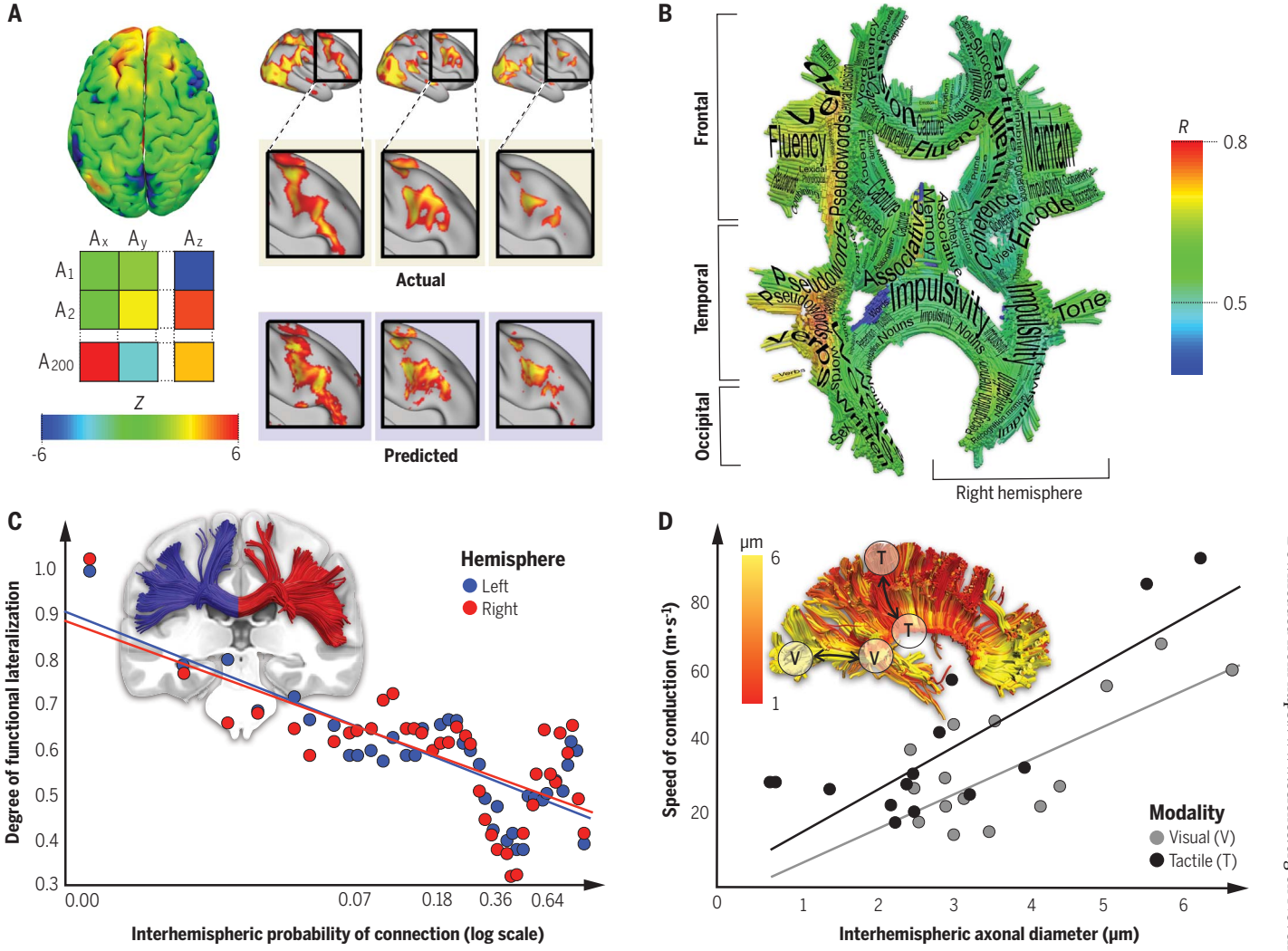

Fig. 2. Functional integration through brain connections as the latent mechanisms determining the function of the brain. (**A**) Functional connectivity (top left) can be summarized in a connectivity matrix (bottom left) that is specific to each individual (*35*). Main trends of functional connectivity can predict individual patterns of task-related activations [right; reproduced with permission from (*13*)]. A, area. (**B**) Similarly, main trends of structural connectivity can predict task-related patterns of cortical activations. The statistical association between these two modalities allows projection of the processes involved in the fMRI tasks onto the brain connections [modified from (*23*)]. *R*, goodness of fit. (**C**) The relationship between functional lateralization and interhemispheric connectivity for the left (blue) and the right (red) hemispheres [modified from (*24*)]. (**D**) Interhemispheric speed of conduction for visual (gray) and tactile (black) modalities is correlated with the strength of their interhemispheric connections [i.e., axonal diameter; modified with permission from (*28*)].

Connectivity unveils interindividual variability

This connectivity variability, or "neurovariability," is critical to the individuals we are. What we know, who we are, and how we communicate with others are ascribed through integrative brain mechanisms. Therefore, to understand the origin of our identity, we need to decipher how connections between brain regions orchestrate our brain functions at the individual level. Accordingly, the strength of communication between brain regions derived from functional connectivity can predict individual differences in brain activation during tasks (Fig. 2A) (*13*). Preliminary work has already created "fingerprints" of the brain's functional connectivity patterns in healthy volunteers that correlate with behavior and cognition [i.e., connectome-based predictive modeling (*34*)]. These fingerprints of connectivity are specific to individuals and predict fluid intelligence (*35*) and creativity (*36*) with impressive accuracy. These correlations with cognition also extend to the differences in the structure of specific brain connections [see Fig. 4A and (*37*)]. For instance, a stronger left arcuate fasciculus seems to facilitate the learning of new words (*38*). These differences affect healthy brain performance and extend to the severity of neurodevelopmental, psychiatric, and neurological symptoms (*37*). Developmental brain connectivity patterns have assisted in diagnosing neurodevelopmental learning deficits (*39*).

In neurology, a stronger arcuate fasciculus facilitates recovery after stroke (*40*), whereas its degeneration has been associated with increased symptom severity (*41*). These observations have led to new anatomical-cognitive models 150 years after the first descriptions of aphasia (i.e., language disorder) as a disconnection syndrome.

Connectivity profiles can change across a life span, leading to increasingly divergent molecular and circuit-level changes that develop over weeks, months, years, and even decades owing to environmental and learning-induced plasticity mechanisms. A good example is literacy, which alters brain connections between the visual and the auditory system even when acquired later in life (*42*). Indeed, plasticity mechanisms can limit long-term cognitive predictions, which are based on the fingerprints of brain connections.

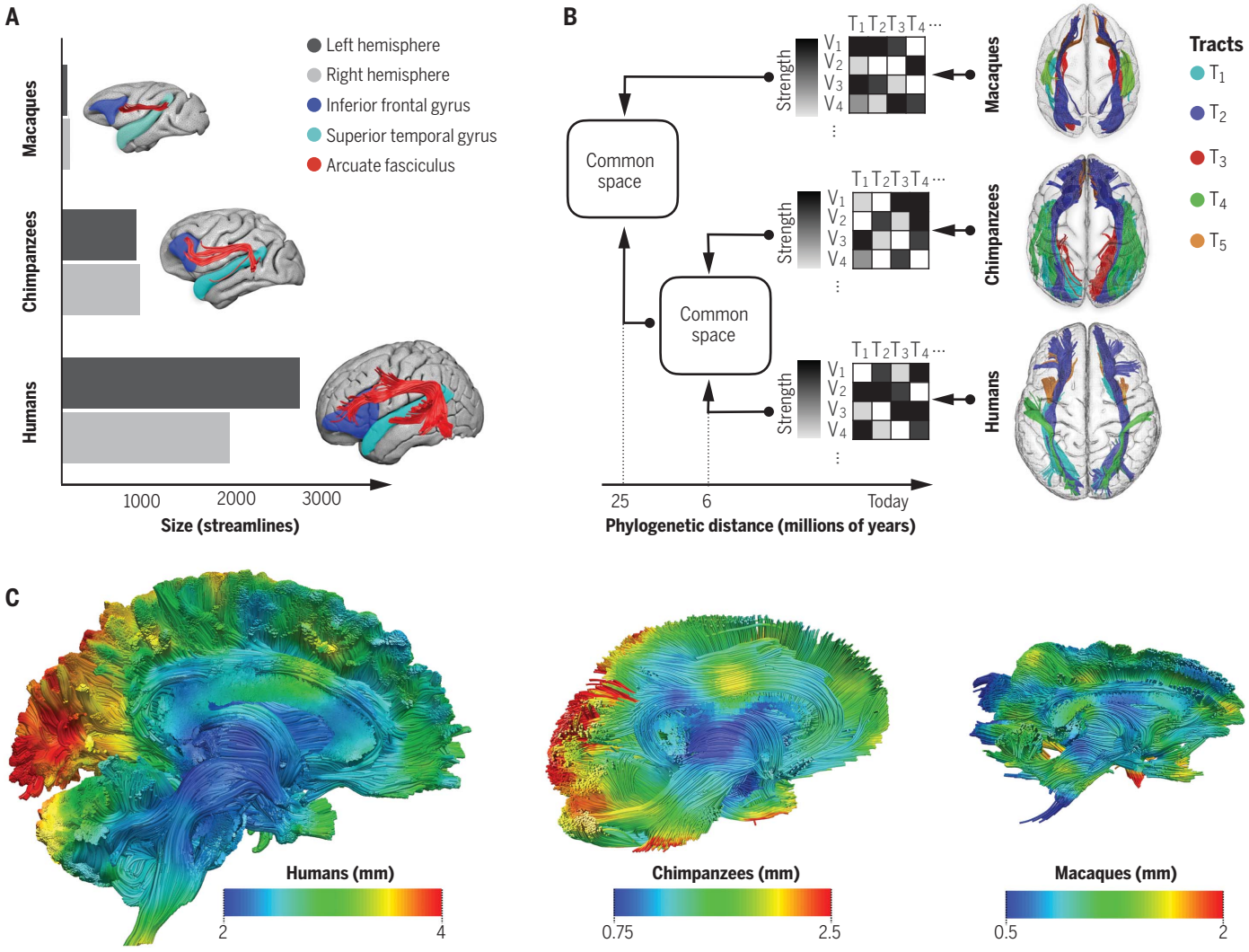

Fig. 3. Connectivity sheds light on mechanisms of brain evolution. (**A**) A comparison of the connections between frontal and temporal brain regions in humans, chimpanzees, and macaques reveals the remarkable expansion and lateralization of the arcuate fasciculus (*29*). (**B**) The extraction of a reliable connectivity profile across species permits the computation of common spaces allowing for an approximation of our ancestors' brains (*30*). In this context, the connectivity profile is defined as the number of streamlines per voxel (i.e., as a surrogate for connectivity strength) for each tract of interest. T, tract; V, voxel; Strength, connectivity strength. (**C**) Connectivity variability (i.e., average white matter deformation required to match a common species-specific template) reveals that the same variability that makes us individually different from each other is also at the root of our differences from our ancestors and our closest evolutionary relatives [modified from (*33*), thanks to data openly available at http://www.chimpanzeebrain.org]. mm, millimeters.

Importantly, while the identification of predictive biomarkers holds vast potential for changing the health of individuals and populations, it also bears fundamental ethical risks and moral challenges (e.g., treatment of predicted brain disease that may never manifest or withholding treatment on the basis of recovery predictions). Overall, these recent studies put forth evidence demonstrating that new behavioral patterns and cognitive functions can arise from even small changes in the interaction between brain regions via their connections.

Functional disintegration through disconnection

Drastic disruptions of brain interactions [i.e., disconnections (*18*)] manifest secondary to pathologies and can induce long-lasting functional symptoms. For instance, a disconnection between visual and language networks leads to irremediable alexia [i.e., inability to read (*43*)]. Although advanced neuroimaging can identify disconnections, these methods are not yet systematically available across the clinical sector. Therefore, new indirect methods that use a priori knowledge of connections (DWI or fMRI) derived from the highest-resolution datasets to estimate disconnection profiles after a brain injury are needed to reliably and statistically map the association between disconnection and symptoms (*44*). In doing so, it is possible to reevaluate classical clinical neuroanatomical phenomena within brain networks and understand the critical contribution of connections to the realization of functions. These new methods can even demonstrate that clinical-anatomical lesion studies in neuroscience's most famous cases can be extended to a disconnection paradigm. This new paradigm shows the networks considered functionally engaged for emotion and decision-making (Phineas Gage), language production (Louis Victor Leborgne), and declarative memory (Henry Molaison) in the healthy population (Fig. 4B) (*45*). Hence, consideration of brain connections appears to reconcile brain lesion studies with functional neuroimaging in healthy volunteers and provides a more comprehensive biological interpretation of clinical

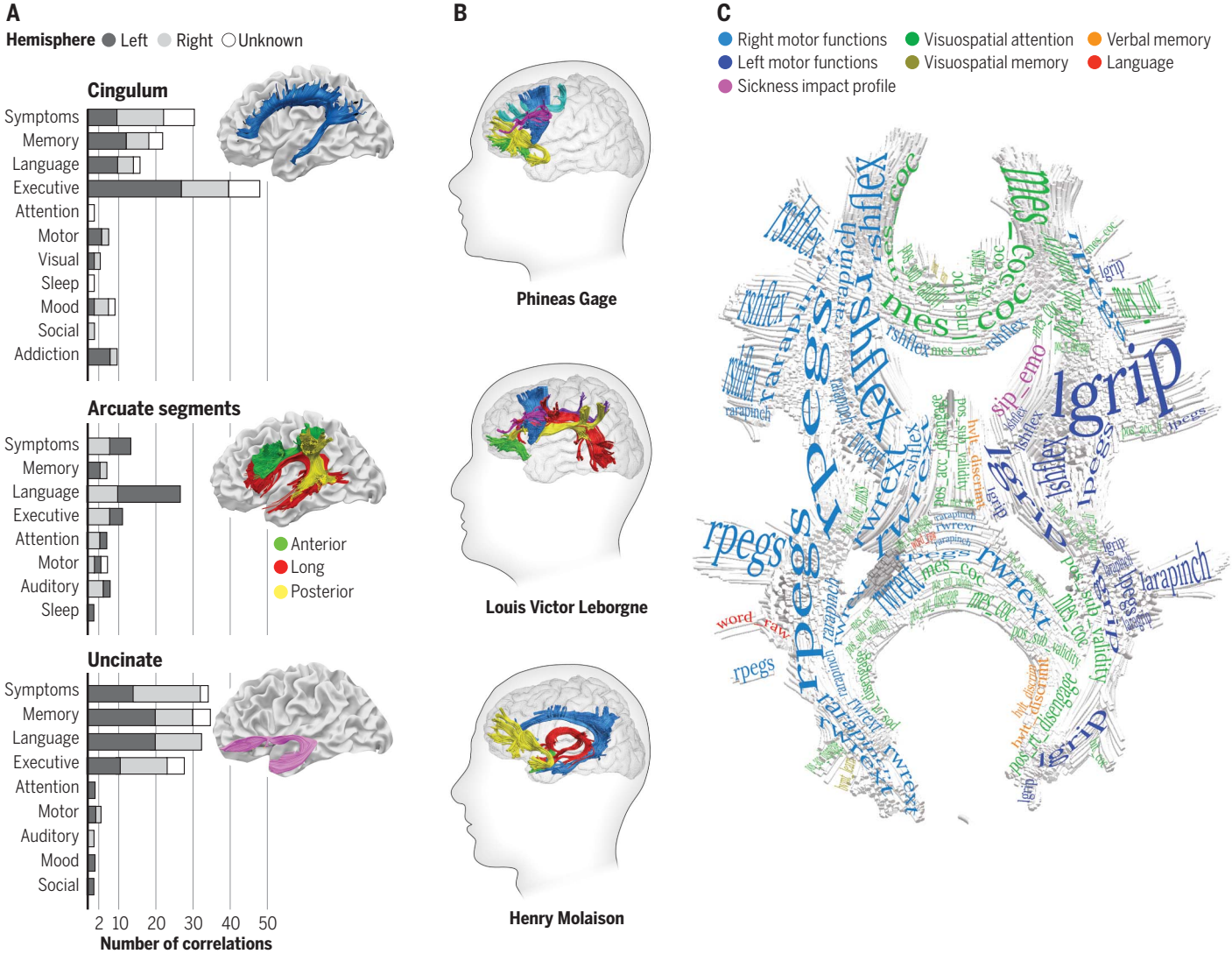

Fig. 4. Disintegration of brain functions through disconnections. (**A**) Systematic review of the relationship between variability in brain connectivity, cognitive profiles, and clinical symptoms [modified from (*37*); https://youtu.be/JVOegYHT21w]. (**B**) Connectivity revisiting neuroscience's most famous cases of neurosciences showing the tracts disconnected in classic neurobehavioral syndromes [from (*45*)]. (**C**) Neuropsychological white matter atlas highlighting the disconnection patterns causing loss of function [courtesy of (*47*); http://disconnectomestudio.bcblab.com].

manifestations with regard to the disintegration of brain processes. Further, brain disconnection results usually achieve a higher explanatory power than lesion localization alone (*46*). The disconnection framework has recently been extended to the entire brain to provide the first clinical map of symptoms associated with specific brain disconnections (Fig. 4C) (*47*). Therefore, it would prove beneficial if measures of brain connectivity were translated into advanced standard operating procedures for personalized neuroscience (*48*) that focus on rehabilitation and that support the prediction of symptom recovery while providing new targets for pharmacological treatments. The evidence presented demonstrates that the key to understanding the brain is in the interaction between multiple areas, and the best guide to its constitutional (as opposed to phasic, task-related) interactions is its connecting infrastructure.

Where do we go from here?

Despite the current progress in estimating brain connectivity, new challenges have emerged that will only be tackled by relying on synergetic efforts. First and foremost, no known method can directly measure the activation of connections in the healthy living human brain. Instead, recent indirect approaches statistically project the functional signal from the cortex onto the white matter (*49*). These indirect methods rely on a priori knowledge of the group-level probability of connections between brain regions. However, regardless of the quality of the dataset used to build these priors, axons are ~1 to 6 μm in diameter (*11*), and routine neuroimaging has a minimum resolution of 1 mm^3 in vivo and 200 μm postmortem (*50*). Similarly, monosynaptically connected areas are synchronized with a delay of 2 to 3 ms (*51*), leading to high-frequency synchronization. Yet standard functional connectivity relies on acquisitions with a temporal resolution of 1 s at best. Hence, some level of approximation exists in the estimation of the orientation of fiber populations and the estimation of the communication between brain regions, leaving room for improvement to estimate the connectome (i.e., whole-brain connectivity) accurately.

There is also an urgent need for complementary methods to provide a practical "gold standard" and a proven means of validation for tractography, akin to the BigBrain model (*52*) for cytoarchitecture measures and cortical thickness. Non-neuroimaging methods may get us closer to that goal. Advanced polarized light imaging (*53*) or Nissl-based structure tensor (*54*), for example, can estimate axonal orientation from postmortem tissues. However, these postmortem approaches are limited to two dimensional (2D) in-plane reconstruction and require tremendous effort to produce a whole 3D human brain comparable to BigBrain. Preliminary work already demonstrates that such an attempt is possible in macaques, and efforts are underway in humans (*55*). Future progress will serve as a cornerstone for improving structural and functional connectivity methods. These new datasets can validate current neurobiological approximations—such as axonal diameter, neurite density, the extent of myelination, information flow, or synaptic complexity at the whole-brain level—derived from neuroimaging. This step is fundamental to ensure that connectivity matrices are reliably translatable to the clinical realm and lead to advances in therapeutic interventions.

Going forward, we need to consolidate these new concepts by developing dedicated software, which provides us with additional resources to sharpen our observations. These developments will include, for example, tools that can represent high-dimensional data in the same latent space as anatomical information across scales (cells, voxels, circuits), across species (macaque, chimpanzee, human), and across imaging modalities (tracing, tractography, polarized light imaging), while accounting for neurovariability at the individual level to capture the factor interactions. To do so, researchers ought to create professional networks, integrate ideas, and share data openly. Together, these endeavors will push brain connectivity research to integrate across imaging modalities (e.g., functional white matter), formulate new frameworks (e.g., neurovariability), and foster our understanding of brain development and evolution (comparative neuroimaging and neuroecology). This joint effort will push our current frontiers and lead to advanced neuroimaging methods, personalized anatomical models, and clinical impact. Hence, it will take an integrative system of people (research consortium) to decipher this complex system within us all and discover the emergent properties of the brain.

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