Opinion

Large-Scale Gradients in Human Cortical Organization

Julia M. Huntenburg,[1,2,*] Pierre-Louis Bazin,[3,4,5] and Daniel S. Margulies[1,*]

Recent advances in mapping cortical areas in the human brain provide a basis for investigating the significance of their spatial arrangement. Here we describe a dominant gradient in cortical features that spans between sensorimotor and transmodal areas. We propose that this gradient constitutes a core organizing axis of the human cerebral cortex, and describe an intrinsic coordinate system on its basis. Studying the cortex with respect to these intrinsic dimensions can inform our understanding of how the spectrum of cortical function emerges from structural constraints.

The Significance of Cortical Location

For more than a century, neuroscientists have studied the cerebral cortex by delineating individual **cortical areas** (see Glossary) and mapping their function [1]. This agenda has substantially advanced in recent years, as automated **parcellation** methods improve and data sets of unprecedented size and quality become available [2–4]. Nevertheless, our understanding of how the complex structure of the cerebral cortex emerges and gives rise to its elaborate functions remains fragmentary. To complement the description of individual cortical areas, we propose an inquiry into the significance of their spatial arrangement, asking the basic question: Why are cortical areas located where they are?

Early formulations of this question date to theories from classical neuroanatomy [1,5–7]. They state that the spatial layout of cortical areas is not arbitrary, but a consequence of developmental mechanisms, shaped through evolutionary selection. The location of an area among its neighbors thus provides insight into its microstructural characteristics [6], its connections to other parts of the brain [7], and eventually its position in global processing hierarchies [8]. Consider, for example, the well-researched visual system of the macaque monkey [9,10]. Along the visual hierarchy, low-level visual features are increasingly abstracted and integrated with information from other systems. Traditionally, areas are ordered based on their degree of microstructural **differentiation**, and the classification of their connections as feedforward or feedback [11]. The framework we advocate emphasizes that an area's position in the visual processing hierarchy – and thus many of its microstructural and connectional features – is strongly related to its distance from the primary visual area [12,13].

More generally, we propose that the spatial arrangement of areas along a global gradient between **sensorimotor** and **transmodal** regions is a key feature of human cortical organization. A gradient is an axis of variance in cortical features, along which areas fall in a spatially continuous order. Areas that resemble each other with respect to the feature of interest occupy similar positions along the gradient. As we will point out, there is a strong relationship between the similarity of two areas – that is, their relative position along the gradient – and their relative position along the cortical surface. This important role of cortical location prompts a new perspective in which we try to understand the cerebral cortex with respect to its own, intrinsic dimensions.

[1]Max Planck Research Group for Neuroanatomy & Connectivity, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstrasse 1a, 04103 Leipzig, Germany
[2]Neurocomputation and Neuroimaging Unit, Department of Education and Psychology, Free University of Berlin, 14195 Berlin, Germany
[3]Social Brain Lab, Netherlands Institute for Neuroscience, Meibergdreef 47, 1105 BA Amsterdam, Netherlands
[4]Spinoza Centre for Neuroimaging, Meibergdreef 75, 1105 BK Amsterdam, Netherlands
[5]Departments of Neurology and Neurophysics, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstrasse 1a, 04103 Leipzig, Germany

*Correspondence:
huntenburg@cbs.mpg.de
(J.M. Huntenburg) and
margulies@cbs.mpg.de
(D.S. Margulies).

Toward this goal, we will first review converging findings on cortical microstructure, connectivity, and gene expression, which point to a dominant sensorimotor-to-transmodal gradient of cortical organization. Next, we will explain how this gradient can help us understand how the spectrum of cognitive functions arises from cortical structure. Finally, we will propose a gradient-based intrinsic coordinate system of the human cerebral cortex.

A Sensorimotor-to-Transmodal Gradient of Cortical Organization

As will be outlined in the following section, there is now comprehensive evidence for a global gradient in human cortical organization, which spans between primary sensorimotor and transmodal regions, and is reflected in cortical microstructure, connectivity, and gene expression. While these cortical features have previously been used to delineate discrete areas, the concept of an overarching gradient does not discount the existence of such areas, but moves their respective spatial relationships into focus.

Cortical Microstructure

The theory of cortical gradients is rooted in classical neuroanatomy (e.g., [1,5–7]). In these studies, histological sections of postmortem brains are examined for the distribution of cells (**cytoarchitecture**) or myelinated fibers (**myeloarchitecture**) in horizontal layers of the cortical sheet. While this labor-intensive approach provides a detailed account of cortical microstructure, the resulting descriptions typically remain qualitative and observer dependent (but see [14]). A more recent line of research takes a simplified view of cortical microstructure by reducing it to a single quantity: the number of neurons within a unit of surface area [15–18]. These studies have demonstrated a rostrocaudal gradient in neuron number in the cortices of a broad range of mammalian species, including several rodents, marsupials, and non-human primates. Neuron numbers are generally high in caudal portions of the cortex, such as the occipital lobe, and gradually decrease toward more rostral regions. This rostrocaudal organization in neuron number aligns with known neurodevelopmental gradients in the mammalian cortex and has been suggested to arise from the temporal sequence of **neurogenesis** [16,19,20] (Box 1).

Box 1. Neurodevelopmental Gradients

It has been suggested that the spatial distribution of cortical features in the adult brain is established by neurodevelopmental gradients. The rostrocaudal gradient in neuron number can be related to timing differences in neurogenesis, which begins uniformly across the cortex, but terminates earlier in rostral regions. In the macaque monkey, neurogenesis ends about 20 days earlier in the rostral pole than in the most caudal regions [61]. Caudal regions thus undergo a higher number of cell cycles, which accounts for the higher number of neurons in these areas. In rostral regions, more time can in turn be devoted to the growth of large neurons that form many connections [62]. The rostrocaudal gradient therefore signifies a shift in computational capacity, from a high number of processing units in caudal regions to a lower number of highly connected units in rostral regions [16]. The gradient is more pronounced in larger cortices [17,20], which have longer developmental schedules, leading to more pronounced differences in neurogenesis termination across areas [19]. In the human cortex a rostrocaudal difference of up to 70 days has been predicted [20].

However, the microstructural gradient in the human cortex appears to not simply be steeper, but to deviate from the rostrocaudal distribution. Cortical development is less understood in humans compared with other mammals and the deviation in the adult cortex could be rooted in spatially more complex developmental gradients. This hypothesis is in line with the observation that gene expression patterns in the human cortex also diverge from the rostrocaudal organization described for other mammals [42]. For example, transmodal regions of the DMN, although located at distant points of the rostrocaudal axis, have similar gene expression patterns. These regions also show protracted developmental expansion and maturation in humans [63]. While much remains to be learned about neurodevelopmental gradients in the human cerebral cortex, such research can help to integrate observations across different cortical features and establish an informed developmental basis for the proposed intrinsic coordinate system.

Glossary

Cortical area: the definition of what constitutes a cortical area is a subject of ongoing debates [2,4]. Most commonly, a cortical area is delineated from neighboring parts of the cortex based on a characteristic cytoarchitecture or myeloarchitecture, connectivity profile, and response to particular stimuli.

Cytoarchitecture: the description of cortical and subcortical organization according to the size and shape of cell bodies and their distribution in horizontal layers of the cortical sheet (e.g., [60]).

Differentiation: cortical areas vary in terms of how clearly the six major cortical layers and their sublayers can be discerned, in their emphasis on infragranular or supragranular layers, and their overall myelin content. Highly differentiated areas generally show a clear laminar structure, emphasis on supragranular layers, and high myelin content.

Intrinsic geometry: properties of a surface that can be measured without reference to another space, for example, the distance along a surface between two points.

Myeloarchitecture: the description of cortical and subcortical organization according to the density of myelinated fibers and their distribution in radial bundles and horizontal layers in the cortical sheet (e.g., [1]).

Neurogenesis: the process by which new neurons develop from neural stem cells to subsequently populate different regions of the brain.

Parcellation: division of the cortex or subcortical structures into typically discrete areas or networks on the basis of differences, for example, in microstructural features, connectivity, or functional properties (e.g., [3]).

Resting-state functional connectivity: brain activity is measured in the absence of explicit task demands and functional connectivity is inferred from the temporal correlation of low-frequency fluctuations across brain regions.

Seed region: region with reference to which a particular measure, for example, connectivity, is calculated.

Sensorimotor areas: collective term for areas that respond to sensory

In some areas neuron numbers deviate from what would be anticipated given their location along the rostrocaudal gradient. For example, elevated neuron numbers have been reported in rostrolateral regions mapping to putative primary somatosensory cortex in multiple species [15,16,18]. Such observations raise the question of whether regular spatial patterns beyond the rostrocaudal gradient can be identified in cortical microstructure. In particular when considering the human cortex, a simple rostrocaudal gradient appears insufficient to explain its microstructural organization.

There is little quantitative data on the distribution of neuron numbers in the human cortex. However, recent advances in high-resolution and quantitative MRI [21,22] together with improved processing tools (e.g., [23,24]) facilitate noninvasive assessment of microstructural features in the human brain. MRI only provides indirect measures of microstructural components, and its spatial resolution is still low compared with histological methods. However, MRI does not require slicing of the brain tissue and thus is ideally suited to capture global gradients in three-dimensional space.

MRI studies of the human cerebral cortex have provided evidence for a microstructural gradient that is anchored in sensorimotor regions and radiates toward higher-order areas in the parietal, temporal, and prefrontal cortex. For example, MRI measures that are sensitive to intracortical myelin have revealed a pattern of high myelin content in primary sensorimotor regions, which systematically decreases toward transmodal areas in parietal, temporal, and particularly prefrontal cortex [3,25–28] (Figure 1A). A similar spatial distribution has been described for MRI-based measures of cortical thickness [12] and myelinated thickness [29]. Cortical thickness coarsely tracks changes in cytoarchitecture [30] and myelin content [25], and can be viewed as a pragmatic surrogate for cortical microstructure [12].

Thus, a rostrocaudal gradient explains much of the spatial variation of cortical microstructure in the mammalian cortex. However, microstructural features in the human cortex depart from the simple rostrocaudal distribution and reveal a spatially more complex sensorimotor-to-transmodal gradient.

Macroscale Connectivity

While cortical microstructure is mostly used to describe local properties of individual areas, studies investigating cortical connections focus on the relationship between areas. Connectivity analyses have often taken the form of dividing the cortex into discrete networks of strongly interconnected areas, but recent studies have demonstrated continuous spatial patterns of connectivity in the human cerebral cortex [31–37]. These studies simplify the complex connectivity matrix – representing how each cortical area is connected to every other area – to a small set of connectivity gradients.

One method of simplification is to select a **seed region** and quantify its connectivity to every other cortical location. When selecting seeds in the different primary sensorimotor areas, gradients of decreasing connectivity strength from each of these seeds converge in multimodal integration areas, such as the anterior cingulate cortex and the occipitotemporal junction, and finally reach transmodal regions of the default mode network (DMN) in the medial prefrontal, posterior cingulate, and temporal cortex [31,32].

In a more data-driven approach, connectivity gradients can be obtained by identifying the main axes of variance in the connectivity matrix [33–37] (Box 2). Each of these axes

input in a single modality (visual, auditory, or somatosensory) as well as motor areas.
Spatial receptive fields: the region of sensory space in which a stimulus will modify the response of a particular neuron.
Supragranular: the superficial aspect of the cortical sheet (layer I–III), which is located external to the internal granular layer (IV).
Temporal receptive windows: the time window in which a newly arriving stimulus will modify processing of previously presented information.
Transmodal areas: cortical areas whose activity is not specific to a single modality of sensory input or motor output.
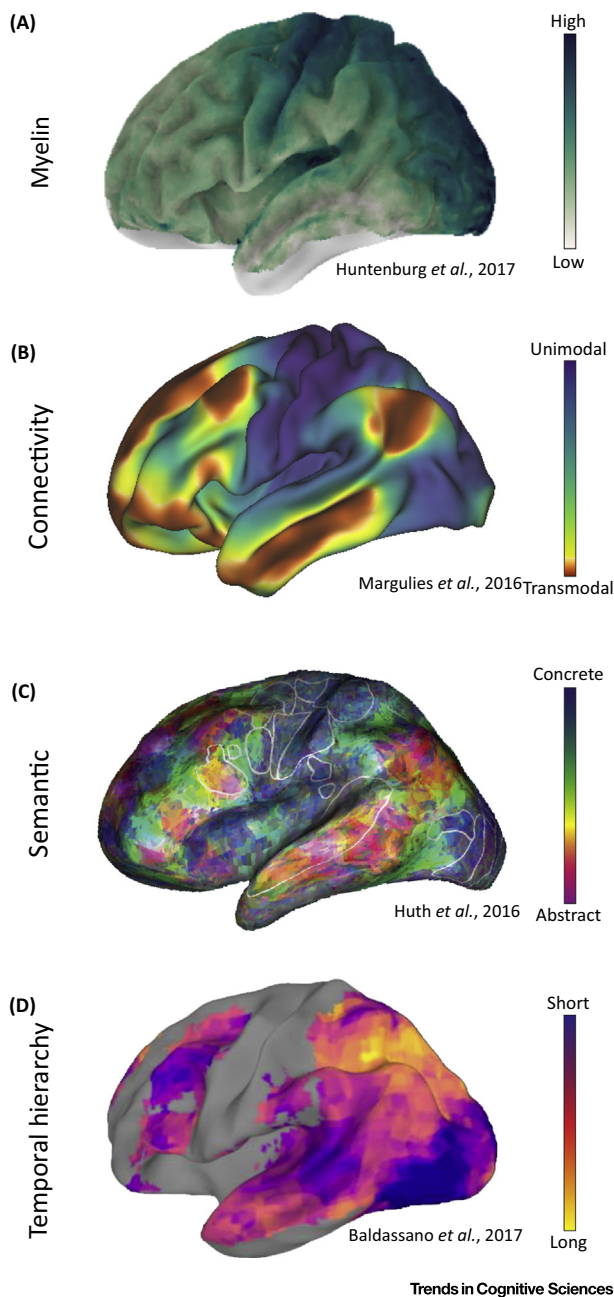
Figure 1. A Sensorimotor-to-Transmodal Gradient Based on MRI Data of the Human Cerebral Cortex. A basic sensorimotor-to-transmodal organization is apparent in different cortical features in the human cerebral cortex as assessed with MRI. (A) Intracortical myelin increases along the sensorimotor-to-transmodal gradient (regions with low signal quality are masked) [25]. (B) The main variance in functional connectivity patterns spans between primary sensorimotor areas and transmodal regions of the DMN. The connectivity gradient does not have a unit, but it is strongly related to a spectrum of concrete-to-abstract cognitive domains [35]. (C) The map shows a superposition of the first three semantic category-processing gradients. The largest axis of variation separates perceptual and physical categories in sensorimotor areas from more abstract concepts in transmodal regions [46]. (D) The length of events that are represented in a given area, here extracted from movie-watching data, varies from short events in sensory areas to long events in transmodal regions (only patterns with high between-subject consistency are shown, for example, somatosensory regions did not respond consistently to auditory–visual input) [53].

represents a gradient, along which cortical locations are ordered according to their similarity in connections to the rest of the cortex. In line with the gradients emerging from primary sensorimotor seeds, the main axis of variance in human **resting-state functional connectivity** data is captured by a principal gradient that spans from primary sensorimotor areas to the transmodal peaks of the DMN [35] (Figure 1B). A corresponding gradient was found in the macaque monkey cortex based on anatomical connectivity data from tract-tracing studies [35].

> **Box 2. Extracting Gradients from High-Dimensional Cortical Data**
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> In the analysis of some cortical features more than one value is assigned to each cortical location. Examples are connectivity data, functional coactivation, gene or receptor expression, depth-resolved microstructure, and in particular multimodal data sets combining several of these features [3,4]. To extract intelligible information from such high-dimensional data, methods for dimensionality reduction are required.
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> One common approach is to group cortical locations into larger parcels based on feature similarity. This approach is efficient but typically imposes hard cut-offs between and homogeneity within parcels. By treating parcels as discrete, independent entities the resulting representations fail to capture more gradual changes and overarching spatial relationships [64].
>
> Gradient approaches instead find the main axes of variance in the data through decomposition or embedding techniques. The original dimensions of the data are replaced by a set of new dimensions, chosen so that most of the variance in the data is captured by just a few of these dimensions. This can drastically reduce the number of dimensions that are required to represent the data, with few assumptions on its internal organization. Often, the new dimensions are inherently ordered, so that the first dimension explains most of the variance in the data (it is sometimes called dominant), the second dimension explains the second most variance, and so on.
>
> Each cortical location can now be described by a set of values reflecting where it falls along the new dimensions. Each dimension is a continuous representation of one aspect of cortical organization, in other words, a large-scale cortical gradient. A set of gradients derived from the same data represents superimposed aspects of cortical organization, which often cannot be captured in a single dimension or a discrete parcellation. Sometimes these different aspects are straightforward to interpret. For example, decomposition of primary visual cortex functional connectivity yields two dominant gradients, each reflecting a different aspect of retinotopic organization – eccentricity and polar angle [37]. Other times, the spatial distribution of different superimposed gradients is less obviously related to known anatomical or functional properties and their interpretation can be more challenging [25].

This principal connectivity gradient is closely related to the **intrinsic geometry** of the cortex. When considering the distance along the cortical surface, locations in the transmodal cortex, corresponding to one extreme end of the gradient, are maximally distant from unimodal sensorimotor regions at the other end of the gradient [35]. This spatial relationship is confirmed across the human and macaque monkey [35,38] as well as mouse cortex [38], revealing the crucial role of area's spatial location for cortico-cortical connectivity patterns. In addition, the spatial layout of the principal gradient aligns with the human microstructural gradient described in the previous section. A direct comparison of the principal gradient of functional connectivity and intracortical myelin content revealed a systematic spatial relationship [25]. Global connectivity patterns thus reveal a sensorimotor-to-transmodal gradient that is strongly related to a gradient in local microstructural features and the intrinsic geometry of the cortex.

Gene Expression

During brain development, molecular gradients constitute important cues and constraints for the emergence of different structures by influencing local patterns of gene expression. While differential gene expression is most pronounced during prenatal development [39] and between subcortical structures [40], substantial spatial variation has also been described within the adult human cerebral cortex [40–43].

Similar to connectivity data, much of the variation in gene expression patterns across cortical areas can be captured in a small set of spatial gradients (Box 2). A dominant gradient of gene expression patterns was found to separate primary visual, somatomotor, and auditory areas on one end from transmodal temporal and frontal areas on the other [40]. This gradient is strongly related to spatial distance; in other words, regions that are close in space tend to have similar gene expression patterns.

In addition, gene expression similarity is related to connectivity [41]. Despite the basic relationship between spatial proximity and gene expression similarity, even distant regions can resemble each other in their gene expression patterns if they share long-range connections. This is particularly true for a set of genes enriched in the **supragranular** layers of the human cortex, from which most cortical connections emerge [42,43]. Expression of these genes differs for example between sensorimotor networks and the DMN, while even distant DMN regions show similar expression patterns. Regions in the dorsal attention network, which are spatially interspersed between sensorimotor and DMN regions, show intermediary expression patterns between those two extremes [42].

Similar to microstructure and connectivity, much of the spatial variation in gene expression patterns in the human cerebral cortex thus occurs along a gradient between sensorimotor and transmodal regions. Gene expression similarity between cortical locations is related to at least two factors: their spatial proximity and the existence of long-range connections between them.

Functional Processing Hierarchies

The spatial arrangement of human cortical areas in a sensorimotor-to-transmodal gradient is reflected in microstructure, connectivity, and gene expression. What are the implications of this structural gradient for understanding cortical function? We propose that this order provides a structural scaffold from which functional processing hierarchies emerge.

While processing hierarchies are typically described in sensorimotor systems (e.g., [9,10]), they have been proposed to extend to transmodal association areas [8,44,45]. In support of this view, spatial gradients of functional integration ranging from unimodal to transmodal areas have recently been described in the human cortex [35,46]. A study mapping semantic category processing revealed a set of superimposed semantic gradients, which smoothly vary across the entire cortex [46]. The principal semantic gradient spans from concrete perceptual and quantitative descriptions, mapping to sensorimotor areas, to abstract category representations related to emotions and social interactions in transmodal regions (Figure 1C).

Similarly, the principal gradient of functional connectivity tracks a functional hierarchy from primary sensory processing to higher-order functions such as social cognition [35]. As described before, the transmodal peaks of this processing hierarchy in regions of the DMN are maximally distant from landmarks in primary cortical areas. It is an intriguing hypothesis that this spatial separation from regions governed by direct perception and action enables the DMN to perform its commonly ascribed functions relating to information integration and abstraction [35,47].

A Temporal Hierarchy Links Structural Gradients and Functional Specialization

The spatial distribution of global functional processing hierarchies overlaps with large-scale spatial trends in microstructure, connectivity, and gene expression. However, this observation alone does not explain how distributed cortical functions emerge from structural gradients. A potential link is a processing hierarchy in the temporal domain, which emerges from microstructural features and long-range connections, and gives rise to distributed functional specialization.

A recent line of research introduced the concept of **temporal receptive windows** – in analogy to **spatial receptive fields** – reflecting the time window in which previously presented information can affect the processing of a newly arriving stimulus [48–53]. The length of

temporal receptive fields was found to vary hierarchically from primary sensory areas, tracking fast changes of a scene on the order of milliseconds to seconds, to transmodal association areas, which encode slowly changing states of the world, complex concepts and situations, and integrate information across seconds, minutes, or longer (Figure 1D). The temporal integration hierarchy is related to a gradient in intrinsic dynamics. Areas with longer temporal receptive fields show slower resting-state fluctuations in human electrocorticography [51] and functional MRI data [54], as well as in single neuron spike trains in the macaque monkey [55].

The cortical spectrum of intrinsic dynamics, and thus the temporal integration hierarchy, naturally emerges from spatial gradients in simple microstructural features and long-range connectivity. This was recently demonstrated in a computational model of the macaque monkey cortex, which combines a local gradient in spine density with a realistic pattern of long-range connections between areas [56]. When a brief stimulus or white noise (representing intrinsic activity) is input to the primary visual or somatosensory areas of this model, a hierarchy of processing timescales emerges: the response is propagated through the network and increasingly integrated over time, so that brief transient activity is observed in early sensory areas, while higher level multimodal and transmodal regions show slow, persistent responses.

Crucially, the temporal hierarchy no longer aligns with empirical findings when the connection patterns are scrambled. The authors conclude that the presence of long-range connections allows for distant regions to influence each other's dynamics [56]. This accounts for cases such as the frontal eye field, which is low in the microstructural hierarchy, but displays comparably slow intrinsic dynamics due to its strong connectivity to a set of high-level association areas.

An Intrinsic Coordinate System of the Cerebral Cortex

A picture thus emerges of an organizing gradient from sensorimotor to transmodal regions, establishing an axis along which all areas of the cerebral cortex can be situated. We propose that this gradient constitutes the core dimension of an intrinsic coordinate system of the human cerebral cortex. Our approach is inspired by the concept of a natural coordinate system of the vertebrate central nervous system (CNS) [57]. Instead of using Cartesian coordinates, the natural coordinate system describes CNS organization along three built-in dimensions: the curved long axis of the neural tube and two limiting curved planes. These organizing axes manifest themselves during CNS development through the orientation of blood vessels and fibers, and the migratory paths of neurons. While simple rostrocaudal patterns in the cerebral cortex align with the long axis of the vertebrate CNS natural coordinate system, we have presented evidence that the core axis of the human cerebral cortex deviates from such rostrocaudal organization. We thus borrow from the basic idea of the natural coordinate system – to use a structure's intrinsic, naturally occurring axes for describing its organization – and apply it to the specific case of the human cerebral cortex. This approach diverges from the common practice in human neuroimaging, to describe cortical locations with respect to their precise position in space. While such spatial coordinates are often arbitrarily imposed by the measurement technique, intrinsically defined coordinates have the potential to indicate the relative position of a cortical location along functional hierarchies and gradients of structural features, thus reflecting the underlying organization of the cortex itself.

We use the term 'intrinsic coordinate system', rather than 'natural coordinate system', to differentiate our proposition from the original concept by Nieuwenhuys and Puelles [57]. While the natural coordinate system is directly deduced from detailed knowledge about CNS development, the gradients discussed here are inferred from various, often indirect, measures

of cortical organization in the adult brain, and retrospectively associated with developmental processes. We do not wish to imply that the intrinsic coordinate system of the cerebral cortex is categorically different from the natural coordinate system of the CNS. By contrast, we assume that eventually, the developmental processes that establish cortical gradients will be uncovered and facilitate an integration between both coordinate systems.

The core axis of the intrinsic coordinate system we propose is the sensorimotor-to-transmodal spatial gradient. This axis reflects a functional spectrum ranging from direct perception and action to integration and abstraction of information. However, it does not account for the functional specialization of different sensory modalities: visual, auditory, somatosensory, and motor regions are all grouped together. While we have focused on the sensorimotor-to-transmodal gradient throughout this article, there is substantial evidence for an additional axis in various cortical features that differentiates between the sensorimotor modalities. A secondary gradient of connectivity in the human and macaque monkey cortex separates visual regions at one end of the gradient from somatomotor and auditory regions at the opposite end [35]. A similar organization has been observed for a secondary gene expression gradient [40]. Recent approaches to MRI-based cortical microstructure, that take into account the laminar architecture of the cortical sheet, also reveal additional differentiation between modalities. For example, the distribution of MRI-based myelin across the cortical depth differs between visual and somatomotor regions [58], in line with well-established histological findings [1]. Finally, it has been proposed that a second dimension in the functional domain distinguishes hierarchies originating from different sensory modalities, which are dynamically selected based on the current input [56]. In line with previous models of cortical organization [8], the distinction between sensorimotor modalities offers an additional axis of differentiation that can be incorporated into the intrinsic coordinate system of the human cerebral cortex.

One of the challenges is how to construct the intrinsic coordinate system concretely. Rather than preferencing one specific cortical feature over another, we propose to take advantage of the observation that the distribution of various cortical features is strongly linked to the intrinsic geometry of the cortex. As illustrated in Figure 2, the first dimension of the intrinsic coordinate system can be constructed from the spatial distance along the cortical surface from transmodal regions to primary areas. In the second dimension, each cortical location is described by its relative distance from morphological landmarks in primary sensorimotor areas. It is thus possible to establish a coordinate system based on the intrinsic geometry of the cortex that accommodates gradients in multiple structural and functional features. The proposed coordinate system is only an initial working model, and the number and exact configuration of its dimensions remain to be resolved. However, this model provides the foundation to explore both consistency and variation across features and individuals, in the quest of an organizational template of the human cerebral cortex.

A distance-based intrinsic coordinate system constitutes a novel research agenda with diverse applications and new methodological and conceptual challenges (see Outstanding Questions). The intrinsic coordinate system provides a common space to integrate observations across time points, measurement modalities, subjects, and even across species. Pioneering studies have shown that aligning functionally equivalent areas based on individual connectivity gradients [33,34] or functional gradients [59] improves matching accuracy compared with morphological alignment alone. Describing cortical features in terms of large-scale gradients also makes way for novel analytic approaches. For example, spatial statistics have been used to compare superimposed aspects of connectivity, represented by individual gradients, across sessions or subjects [37]. In addition, as basic cortical gradients appear to be conserved across
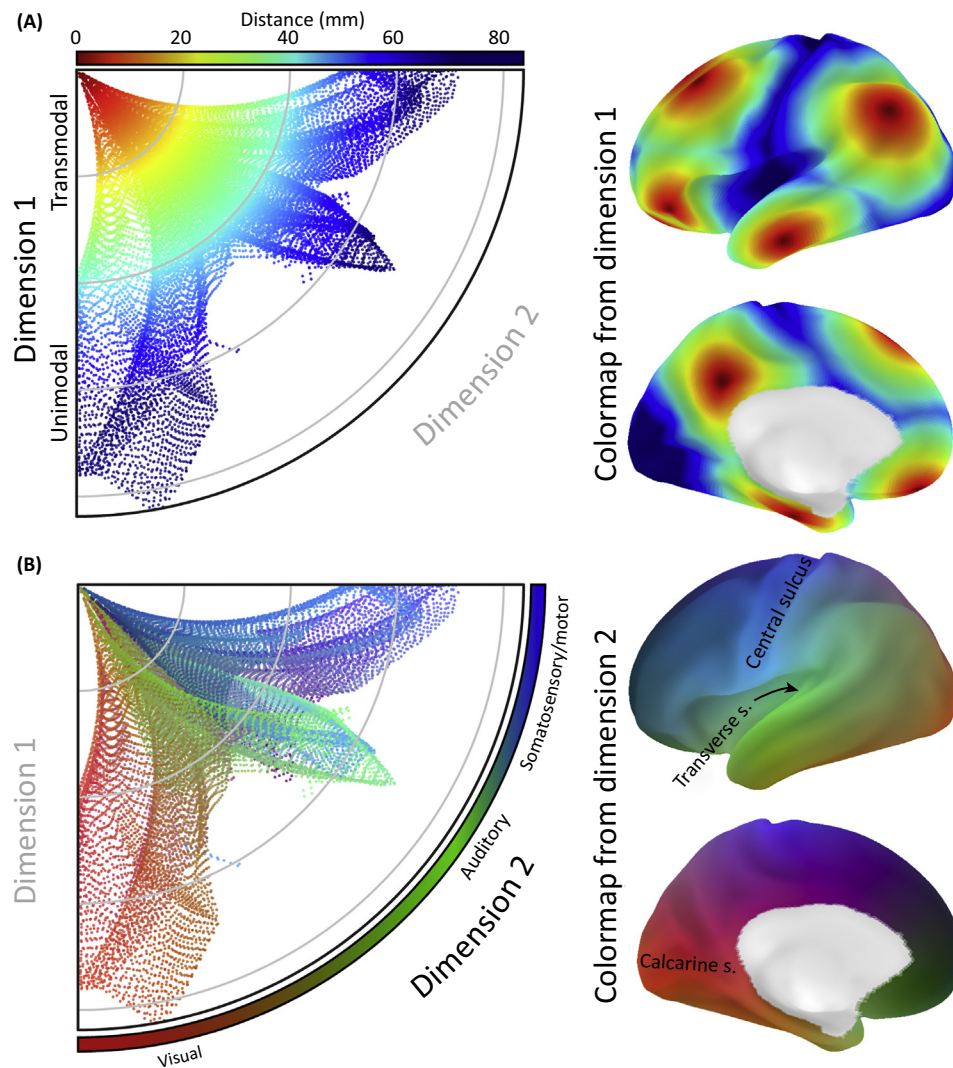
Trends in Cognitive Sciences

Figure 2. Example of an Intrinsic Coordinate System. We propose an intrinsic coordinate system based on the distance along the cortex. Each data point in the intrinsic coordinate space (left) represents a location on the cortical surface (right). (A) Data points are colored according to the first intrinsic dimension. This dimension is given by the distance along the cortical surface between sensorimotor and transmodal regions, represented in a color spectrum from red to blue. In other words, the minimum distance of a cortical location from any of the red transmodal seed regions determines its position along the first intrinsic dimension. In the abstract representation (left), this dimension is represented by concentric circles of increasing size. When displayed on the cortical surface (right) it largely aligns with the feature maps in Figure 1. (B) Data points are colored according to the second intrinsic dimension, which differentiates between the different sensory modalities. The position of a cortical location along this dimension is given by its relative distance along the cortex from three morphological landmarks in primary areas. Each cortical location is assigned an RGB value composed of its proximity to each of these landmarks (calcarine sulcus = red, transverse sulcus = green, central sulcus = blue). That means, the closer a cortical location is to the calcarine sulcus, the higher its R value, and so on. The second dimension is captured by the distance along the arc of the abstract representation of the intrinsic coordinate space (left). s., sulcus.

species [18,35], the intrinsic coordinate system provides a new approach for comparing phylogenetic variation in cortical features. A research agenda based on the idea of an intrinsic coordinate system of the human cerebral cortex thus reinforces the integrations of findings across systems, modalities, and species and their interpretation in the context of cortical development.

Concluding Remarks and Future Perspectives

The spatial arrangement of cortical areas is not arbitrary. An area's position along a core gradient between sensorimotor and transmodal areas reflects its microstructural and genetic features, its connectivity profile, and functional role. Recognizing this relationship introduces a new perspective in which cortical organization is described with respect to its intrinsic dimensions. It takes us beyond the localization of functions to areas and networks, toward an understanding of how the spectrum of cognitive capacities emerges from the spatial arrangement of structural features. Uncovering the neurodevelopmental basis of these intrinsic dimensions, and exploring their convergence and variation across species, has the potential to demystify the emergence of uniquely human cognitive functions.

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Outstanding Questions

Beyond the cerebral cortex, are other brain structures such as the cerebellum or the basal ganglia organized along corresponding large-scale gradients? If so, how do gradients in different structures relate to each other, and can they be unified into a single coordinate system?

What is the best way to align gradients across individuals? When decomposing data from individual subjects, matching the gradients is not trivial. How do we distinguish meaningful interindividual variation from noise?

How many meaningful superimposed gradients constitute the intrinsic coordinate system?

Are the dimensions of the intrinsic coordinate system suitable to represent brain activation patterns across task states? And how stable or dynamic are these dimensions across different conditions?

Are neurological and psychiatric conditions associated with specific alterations in cortical gradients? For example, do stroke-induced lesions cause local disruptions or even global reorganization of cortical gradients? Are developmental disorders reflected in altered gradients?

How do cortical gradients emerge during development and change across the lifespan? Do gradients in different cortical features develop simultaneously, in response to a common underlying mechanism, and are their changes interdependent?

How far do cortical gradients differ across species? Could an adaptive pressure on steeper cortical gradients underlie the evolution toward an extended spectrum of cognitive functions?

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