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Multiscale modeling of cortical gradients: The role of mesoscale circuits for linking macro- and microscale gradients of cortical organization and hierarchical information processing

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ABSTRACT

The gradient concept in neuroscience describes systematic and continuous progressions of features of cortical organization across the entire cortex. Recent multimodal studies revealed a macroscale gradient from primary sensory to transmodal association areas which is linked to increasing representational abstraction along the cortical hierarchy, and which is paralleled by microscale gradients of cytoarchitecture and gene expression profiles. Convergent or divergent evidence from these multimodal studies is then used to support inferences about the existence of one common or multiple scale-specific gradients of hierarchical information processing. This paper evaluates the validity of such inferences within the framework of multiscale modeling. In branches of physics and biology where multiscale modeling techniques are used, the simple averaging of microscale details can introduce errors in macroscale modeling if it ignores structures at the intermediate mesoscales of organization which affect system behavior. Conversely, information about mesoscale structures can be used to determine which microscale details are actually relevant to macroscale behavior. In this paper, I similarly argue that multiscale modeling of cortical gradients needs to take organization of mesoscale circuits into account if it affects the structure-function relation that the models describe. Information about these circuits provides crucial evidence for evaluating inferences from micro- and macroscale data to the role of cortical gradients in hierarchical information processing. My application of the multiscale modeling framework reveals that the gradient concept tracks multiple overlapping progressions of cortical properties, rather than one overall gradient of hierarchical information processing. I support this argument by proposing a mesoscale gradient of connectivity which describes architectural differences between granular and agranular circuits, and which helps us better understand the relation between neural connectivity and hierarchical information processing.

1. Introduction

The neuroscientific concept of gradients describes how features of cortical organization exhibit systematic and continuous progressions that span the entire cortex (Sanides, 1962; Goulas et al., 2018). Classical studies use invasive methods (e.g., histological staining and in vivo tract-tracing) to describe gradients of *microscale* features such as myelo- and cytoarchitecture. Recent data-driven connectomics studies have extended the gradient concept to non-invasive measures (e.g. correlations in activity measured by fMRI), which describe *macroscale* features such as network architecture. Margulies et al. (2016), for instance, discovered that the axis of greatest variance in resting state functional connectivity runs from primary sensory areas via attention networks to the default mode network. This “principal gradient” is assumed to reveal a hierarchy of *representational abstraction*. According to Margulies et al. (2016) representational abstraction is defined by distance from sensory input—how directly/indirectly the network connects to sensory systems—and content heterogeneity—how many sensory modalities and cognitive domains the network represents information from. The principal gradient suggests that representational abstraction is lowest in primary sensory areas which directly represent unimodal environmental inputs, and highest in neocortical association areas which integrate diverse types of information independent of current environmental changes. How does this macroscale hierarchical gradient of functional connectivity relate to microscale gradients of cyto- and myeloarchitecture?

To answer this question, recent multimodal studies have shown that macroscale gradients of functional connectivity are paralleled by several microscale gradients. In humans, the principal gradient is linked to MRI contrasts which are assumed to indirectly reflect intracortical myelin. Neocortical association areas have a lower myelin content than primary sensory areas (Huntenburg et al., 2017). MRI contrast maps reflect this anatomical hierarchy (Burt et al., 2018), even though the sensistivity of the contrasts for detecting myelin is debated (Hagiwara et al., 2018). Researchers have used the convergence or divergence of gradients at different scales to support different inferences about cortical organization. Fulcher et al. (2019) use the convergence of multimodal gradients in mice and humans to infer one overarching, evolutionarily conserved gradient of hierarchical information processing. Similarly, Hilgetag and Goulas, (2020) argue that gradients of myelo- and cytoarchitecture, amongst others, determine macroscale connection patterns which underlie hierarchical processing in the visual system.[1] In contrast,

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[1] In this paper “hierarchy” always refers to the anatomical hierarchy along which the brain activity represents information over increasingly longer time pe-

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Paquola et al. (2019) use the divergence of the principal functional gradient from a microstructural gradient of cytoarchitectonic similarity to infer that default mode and frontoparietal networks support cognitive functions that require great flexibility, such as cognitive control or social cognition. How can we evaluate the validity of such inferences?

In this paper, I propose to evaluate inferences involving the gradient concept by adopting the framework of *multiscale modeling.* Analyses of multiscale modeling in physics and biology emphasize that simply averaging microscale details can introduce errors in modeling macroscale behavior if it ignores structures at intermediate *mesoscales* of organization which affect system behavior (Green and Batterman, 2017; Batterman and Green, 2020). Similarly, although finding direct correlations between micro- and macrostructure is an important first step to better understand cortical organization (van den Heuvel et al., 2015), it can introduce errors if it ignores organization at the *mesoscale* that is relevant to the relation between structure and function in the brain. In neuroscience "mesoscale" is typically defined as the scale of *cortical circuits* (Mitra, 2014). Circuit organization provides crucial evidence to evaluate inferences which connect macro- and microscale gradients to hierarchical information processing. My transposition of the multiscale framework from physics to gradient modeling reveals that micro- and macroscale gradients can vary with different circuit features, such as recurrent excitatory strength, degree of incoming/outgoing connections or interlaminar inhibition. These features are related to different aspects of hierarchical information processing, which this paper tentatively identifies with integration time, flexibility, or representational abstraction. Because scale-specific gradients also terminate in different parts of the cortex, my analysis suggests that the gradient concept describes multiple progressions of cortical properties which only partially overlap, rather than one overall gradient of hierarchical information processing.

The framework developed below advances existing multiscale approaches in three ways. First, it goes beyond network models which apply tools from graph theory to networks at multiple scales (Zednik, 2018), e.g. by using a resolution parameter to detect communities of interconnected brain regions at various sizes (Betzel and Bassett, 2017). Although helpful to detect small communities in functional or structural connectivity data, it is unclear if this approach is sufficient to characterize the mesoscale since it does not specify the internal circuit architecture of nodes within a community (cf. Betzel and Bassett, 2017, p. 73). The mesoscale gradient proposed below alleviates this issue and specifies both circuit architecture and connectivity patterns along the cortical hierarchy, which can be investigated using graph theoretical tools. Second, current multiscale network models lack tools to describe the relation between features at different scales of cortical organization (cf. (Betzel and Bassett, 2017) p. 80). By contrast, the multiscale modeling framework in physics does provide mathematical techniques (boundary conditions and homogenization) to relate upper- and lower-scale modeling of a system (Batterman, 2013). This paper transposes this framework to connectomics by identifying the unique roles such techniques play in relating data from multiple scales of cortical organization. Third, philosophers of science have only analyzed cases in which multiscale modeling is used to explain a particular type of behavior of the target system, e.g. the cracking of steel or bone under macroscopic stress (Wilson, 2017; Green and Batterman, 2017; Batterman and Green, 2020). My analysis of multiscale modeling of cortical gradients shows that in addition to explanation, multiscale techniques are also used to explore the multiscale organization of a system that is only partially understood. This exploratory use can help scientists to discover patterns relevant to many different types of behavior, and to determine which lower-scale features upper-scale data patterns could refer to.

The paper proceeds as follows: Section 2 transposes the multiscale modeling framework from multiscale modeling of macroscale behavior in physical systems to multiscale modeling of cortical organization in connectomics. Section 3 applies this transposed framework to multiscale models which relate cortical gradients to hierarchical information processing. The analysis shows that micro- and macroscale gradients co-vary with different gradients of circuit features which terminate in different parts of cortex. Multiscale models may therefore describe multiple overlapping gradients, related to different aspects of hierarchical information processing. I support my argument by proposing a mesoscale gradient that is based on architectonic differences between granular and agranular circuits (Hilgetag et al., 2019), and discuss its relation to micro- and macroscale gradients.

2. From modeling multiscale physical systems to multiscale models of brain organization

2.1. Studying physical and neural systems at multiple scales

Physical systems and biological systems are both organized at multiple spatial, temporal or kinetic scales. The discussion below focuses on spatial scales of organization, such as spatial scales in a bar of steel (Fig. 1A). At the continuum length scale, steel exhibits elastic behavior, whereas at the atomic length scale, it exhibits a rigid lattice structure. To explain macroscale behavior (e.g. how a steel bar responds to stress), physicists combine continuum and atomic models with models describing mesoscale organization. Inhomogenous mesoscale structures such as dislocations protect the atomic lattice from macroscopic stress, if they can move around freely (Wilson, 2017). Once the dislocations pile up against a cementite wall, however, molecular bonds become exposed to macroscopic stress, which turns the steel bar brittle. To explain the steel bar's response to stress, physicists link together different submodels which describe the behavior of steel at distinct scales.

Consider next the different spatial scales at which neuroscientists describe cortical organization (Fig. 1B). At the macroscale, researchers describe the brain in terms of cortical areas which are connected into whole-brain networks. At this scale, the brain exhibits systematic patterns of slow, low-frequency fluctuations in the blood oxygenation level-dependent (BOLD) signal measured by resting state functional connectivity studies. The principal gradient of functional connectivity describes cortical organization at the macroscale (Margulies et al., 2016, Wang et al., 2019). Stereotypical patterns of anatomical connectivity between cortical areas are also situated at the macroscale (Felleman and Van Essen, 1991). In contrast, at the microscale researchers describe the brain in terms of individual cells or subcellular components. At this scale, the cortex exhibits differences in neuronal density, myelination, gene expression or axonal connectivity. Gradients of cell density (Paquola et al., 2019), gene-expression profiles (Burt et al., 2018; Fulcher et al., 2019) and dendritic spine density (Demirtaş et al., 2019) all describe cortical organization at the microscale. Just as in the case of steel, however, there exist intermediate scales of organization between cortical areas/networks and individual neurons. One such intermediate scale is the *mesoscale of cortical circuits*. At this scale, researchers describe the brain in terms of different *cell types* (e.g. spiny stellate cells in granular layer 4, excitatory pyramidal projection neurons in infragranular layer 5 or inhibitory bouquet cells in supragranular layer 3) and their stereotypical intrinsic connectivity (e.g. layer 5 pyramidal cells connect to layer 3 inhibitory cells). A gradient description specific to this scale, which is proposed in Section 3.2, involves intrinsic connectivity differences based on the spatial extent of granular layer 4 (Beul and Hilgetag, 2015).

The multiscale framework in Fig. 1B agrees with well-known definitions of the microscale as neurons and synaptic connections and the macroscale as brain areas and pathways (Sporns et al., 2005). By con-

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riods, with greater flexibility, and increased degrees of representational abstraction (see Burnston and Haueis, 2021 and section 3.1 for discussion). To avoid confusion, I refrain from using other senses of "hierarchy" such as the brain being a multiscalar hierarchy of nested modules (Hilgetag and Goulas, 2020). This restriction avoids terminological confusion when discussing the question how gradients at multiple scales relate to aspects of hierarchical information processing.

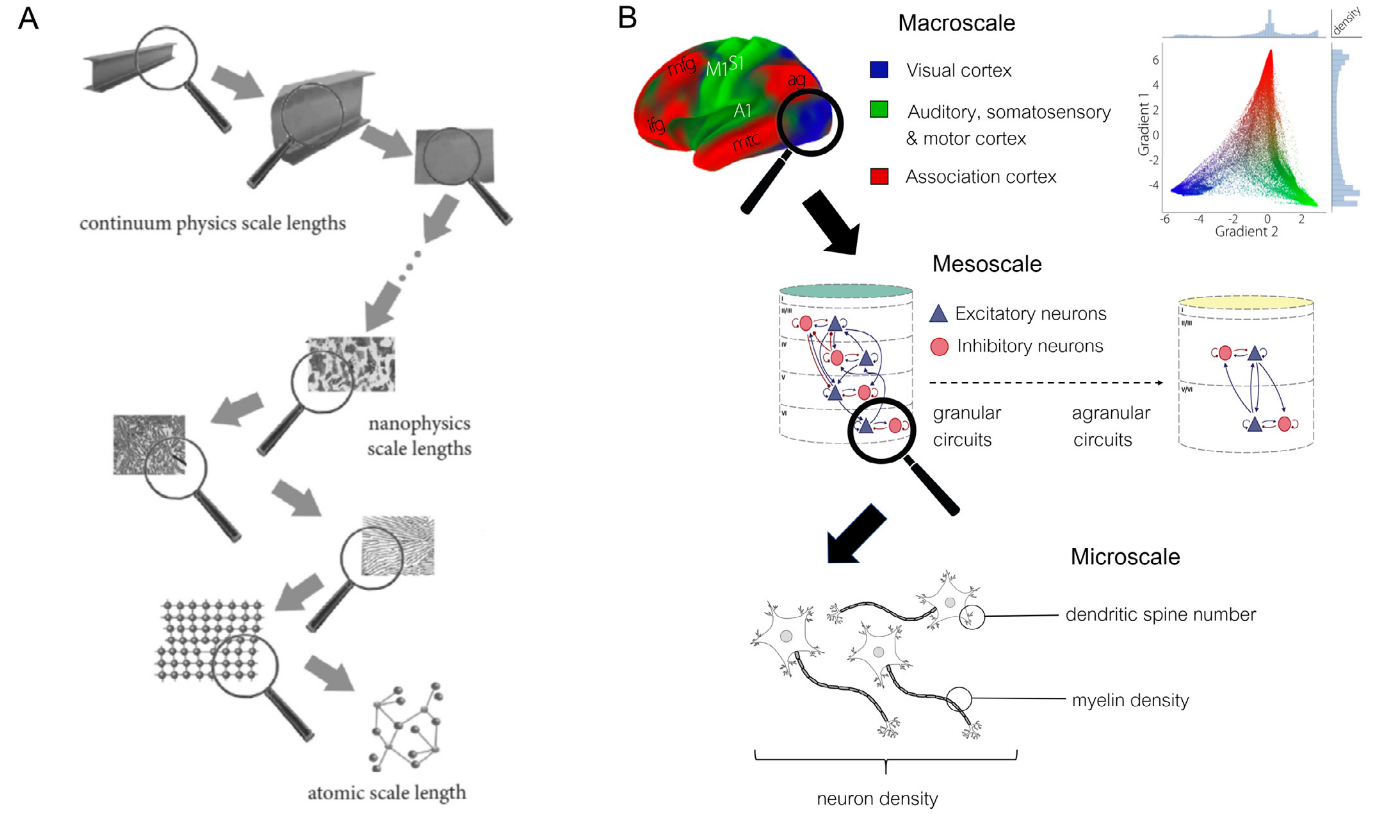

Fig. 1. Framework for multiscale modeling. (A) Physical systems such as a steel bar exhibit different structures and behaviors at characteristic length scales. (adapted from Green and Batterman (2017). (B) Cortical organization exhibits gradients at characteristic length scales. A macroscale gradient of functional connectivity runs from primary sensory to neocortical association areas (adapted from (Margulies et al., 2016) Margulies et al., 2016). A mesoscale gradient of circuit connectivity, proposed in Section 3.2, runs from granular to agranular areas (circuit diagrams adapted from Beul and Hilgetag, 2015). At the microscale, different gradients quantify changes in dendritic spine, neuron and myelin density. .

trast, it is more difficult to define the mesoscale because it is debated what the relevant biological units are. Sporns et al. (2005) propose minicolumns and their connections, but the functional significance of these units is disputed (da Costa and Martin, 2013; Haueis, 2020). By contrast, Mitra (2014) defines “mesoscale” as the transitional length scale at which individual variation becomes negligible while species-typical organizational features such as cytoarchitectonic gradients remain visible. But Mitra’s definition excludes cell types because of our limited knowledge of this mesoscale feature. It therefore does not capture the mesoscale gradient displayed in Fig. 1B, which is based on both cytoarchitectonic and cell-type specific connectivity in cortical circuits (see Section 3.2 for discussion). Additionally, distinctions between different scales are often based on the resolution limits of instruments used to investigate cortical organization (e.g., microscale electrophysiological recordings vs. macroscale fMRI recordings).

Although the multiscale framework developed here does not solve all of these terminological or tool-based differences of using "scale" in neuroscience, it does put these distinctions on a more objective basis. In physics, researchers distinguish scales based on the *dominant behaviors* that a physical system displays at characteristic length scales (Green and Batterman, 2017). Mesoscale information is conveyed in a *representative volume element*, which is defined as the smallest element which is statistically representative of macroscale continuum behavior of the whole, and the largest element that is representative of collective microscale effects on upper-scale parameters (Batterman and Green, 2020). Similarly, although neuroscientists may use the terms “micro”, “meso” and “macro” differently, they still agree that there are important *patterns* or *regularities* in cortical organization that are discernable at characteristic length scales. For example, in the temporal domain, cortical circuits exhibit layer-specific oscillations (Bastos et al., 2015) that are both distinct from low-frequency fluctuations in macroscale networks (Deco et al., 2013) and single neuron spike patterns at the microscale. In the spatial domain, Fig. 1B illustrates that cortical gradients exhibit different patterns at characteristic length scales. The representative volume element at which neuroscientists model mesoscale circuit behavior are 1mm^3 patches of cortex, which is the smallest element representative of macroscale behavior of a cortical area or network, and the largest element representative of collective effects of microscale details, such as the effects of cell or dendritic density on circuit or network activity (Potjans and Diesmann, 2014). While this length scale is based on important regularities and patterns in primary visual cortex, such as sequence regularity of orientation tuning and or cell-type specific vertical connection patterns, it excludes other aspects such as patchy horizontal connections which extend up to 8 mm (Schmidt et al., 2018a).

The transposition of the multiscale modeling framework from physics to connectomics aims to show that researchers require information about mesoscale circuits to properly link micro- and macroscale descriptions of cortical organization. Consider the study of Paquola et al. (2019), which compared the macroscale functional gradient (G_{FUNC}) to a microscale histological gradient (G_{HIST}), which quantifies neuron density in Merker-stained slices of human cortex at the resolution of 100 μm. As mentioned above, they found that G_{FUNC} runs from sensory to neocortical association areas, and G_{HIST} runs from sensory to paralimbic areas. Because Merker stain does not differentiate between different neuron *types*, however, G_{HIST} is insensitive to any cell-type specific differences between mesoscale circuits along each gradient. Do these differences follow G_{HIST} towards paralimbic areas, or G_{FUNC} towards neocortical association areas, or do they run in yet a different direction? According to the multiscale framework developed here, these questions can be answered by taking information about mesoscale circuit architecture in these areas into account. This kind of information is also crucial to evaluate the validity of inferences that connect micro- and macroscale data. For example, Paquola et al.'s inference would receive additional support if circuit organization in neocortical association areas supports more flexible processing than the circuit organization in paralimbic areas. The next section explains why mesoscale information has this crucial role in multiscale modeling.

2.2. *The evidential role of mesoscale information in multiscale modeling*

Unlike existing philosophical accounts, the transposed multiscale modeling framework shows that mesoscale information plays two different roles when used to link microscale details and macroscale patterns. In multiscale modeling of physical systems, mesoscale information is crucial to explain a particular type of macroscale behavior. In connectomics, however, mesoscale information is crucial to determine which anatomical or physiological features underlie a macroscopic data pattern (e.g., functional connectivity). The upper-scale pattern and the lower-scale features are not only relevant to one type of behavior. They are relevant to many different types of brain function. Multiscale modeling is thus used to *explore* the relation between micro- or mesoscale features and macroscale patterns, rather than to explain their role in a particular type of behavior.

To understand this contrast, consider how multiscale modeling is used to explain a particular type of behavior (e.g., a steel bar cracking under repeated macroscopic stress). They describe only mesoscale behavior (e.g., dislocations pile-up at a cementite wall) relevant to explain the macroscale behavior. Rather than searching for microscale details in the entire system (here: brittle molecular bonds), researchers use a mathematical *boundary condition* to restrict microscale modeling to regions where the mesoscale behavior is most likely to occur. Besides using boundary conditions to link upper- to lower-scale models, multiscale modeling also uses the mathematical operation of *homogenization* to incorporate lower-scale information back into the upper-scale model. This operation takes an asymptotic limit to describe the heterogenous mesoscale structure (e.g. disclocations) as a fictitious homogenous material which exhibits the same behavior (Batterman, 2013). The homogenized description can then be used in the macroscale model. Like boundary conditions, homogenization allows physicists to link explanatorily relevant information across scales.

By contrast, mesoscale information plays another role in multiscale connectomic models because they differ in *aim* and *structure* from multiscale modeling in physics. Connectomic models do not explain one type of behavior but instead aim to discover features of brain organization relevant to many different types of brain functions (Ankeny, 2000; Haueis and Slaby, 2017). Neuroscientists can use information from connectomic models to explain different types behaviors of the system. Instead of selecting information based on its relevance to one type of behavior, connectomic models select information based on a *fundamental presupposition* about the organization of the brain (Ankeny, 2000). A fundamental presupposition specifies the relation between neural structure and function in a class of nervous systems. Information in a connectomic model will be relevant to explain the behaviors in any neural system (or subsystem) which realizes the structure-function relationship presupposed in the model. Consider two presuppositions of connectomics models that are commonly used in multiscale modeling of cortical gradients. First, macroscale connectivity models of the macaque visual system classify tract-tracing data based on the fundamental presupposition that differences in laminar connectivity patterns underlie a hierarchy of information processing (Felleman and Van Essen 1991; Section 3.1). Such hierarchical models of the visual system contain information which can be used in explanations of various visual functions, such as motion perception or face recognition (Burnston and Haueis, 2021). Second, consider the mesoscale model of the *canonical microcircuit* or CMC (Fig. 1B, middle). This model selects information based on the fundamental presupposition that *form follows function*, which emphasizes basic commonalities in functional mechanisms across brain areas (Douglas and Martin, 1992). Based on this presupposition, the CMC model posits the smallest number of neuron types and connections consistent with the recorded physiological data (Douglas and Martin 1992, Potjans and Diesmann, 2014). It therefore describes a circuit infrastructure which can underlie a variety of functions, such as direction-selectivity in primary visual cortex (Douglas and Martin 1992, Fig. 15.5) or activity driving eye-saccade behavior in the frontal eye field (Heinzle et al., 2007). Multiscale models of cortical gradients both use hierarchical presuppositions and the CMC as one kind of model of mesoscale architecture (Chaudhuri et al., 2015; Schmidt et al., 2018a). These models also aim to discover features of brain organization that are relevant to different types of cortical functions along the cortical hierarchy (Section 3.1).

In multiscale systems such as the brain, many different features can realize the structure-function relationship presupposed by a connectomics model. Researchers therefore also need *scale-specific modeling assumptions* to link data types to scale-specific features characterized by multiscale gradient modeling. For example: a microscale assumption is that layer-specific differences in histological intensity profiles reflect differences in cytoarchitectonic similarity (Paquola et al., 2019). This assumption links G_{HIST} values to degrees of laminar and cytoarchitectonic differentiation. These features realize the organization presupposed by the structural model, according to which areas with similar cytoarchitecture are more strongly connected than architectonically dissimilar areas.[2] A mesoscale modeling assumption is a modified version of Peters' rule, which states that the probability of a synaptic connection is proportional to the length of the dendrites of a layer-specific neuron type (Potjans and Diesmann, 2014; Schmidt et al., 2018a). This assumption allows researchers to link reconstructions of individual cell morphologies and in-vivo physiological recordings to cell-type specific connectivity patterns (da Costa and Martin, 2013). Finally, a macroscale modeling assumption is that the spatial and connectivity distance from primary sensory areas reflects the degree to which a large-scale network can integrate different types of information independently of transient environmental changes (Margulies et al., 2016). This assumption provides a link between task-independent, low-frequency BOLD-fluctuations and the position of a resting state network along the gradient of increasing representational abstraction. A multiscale model in connectomics combines scale-specific modeling assumptions to link distinct data types to features of brain organization which are relevant to many different types of brain function.

While scale-specific modeling assumptions link data types to features of brain organization, they do not connect these scale-specific types of information to each other. To link information *across* scales, connectomic modelers need an equivalent to upper-scale boundary conditions and homogenized lower-scale descriptions in multiscale modeling in physics. Recall that in the physics case, the function of these mathematical operations was to restrict the modeling domain and select information that is relevant to explain a particular macroscopic behavior (e.g., response to macroscopic stress). In contrast, multiscale connectomics models link information across scales to explore how a macroscale data pattern is relevant to various types of brain functions in different parts of the brain. Instead of restricting the model domain via boundary conditions, they use the macroscale data pattern to *parametrize* the values of a mesoscale model across the entire brain. Similarly, the function of homogenized lower-scale descriptions is not to select information relevant to one macroscopic behavior. Rather the function of homogenization is

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[2] The structural model makes no explicit assumptions about function. It is widely held, however, that structural connections strongly constrain how brain regions can communicate with one another (Pandya et al. 2015). Therefore, the relation between architecture and connections presupposed in the structural model strongly constrain how information is processed in the brain.

to explore what lower-scale feature the upper-scale pattern could *refer* to.

To illustrate the role of parametrization and homogenization in multiscale connectomic modeling, consider another mesoscale model often used in multiscale modeling of cortical gradients. Deco et al. (2013) developed the *mean dynamic field model* (MFM) to explore the link between mesoscale circuit features and macroscale functional connectivity patterns measured by fMRI. The MFM approximates mesoscale circuit activity by looking only at the intra-areal *mean* and interareal *covariance* of the synaptic gating variable *S*. To link this mesoscale model to macroscale functional connectivity patterns, Deco et al. used the Balloon-Windkessel model which translates *S* into the fMRI BOLD signal. They then used empirically observed functional connectivity patterns to *parametrize* the MFM: they systematically varied *w*, the recurrent excitatory strength within the circuit model, and the global coupling factor *G*, which is multiplied with empirically measured structural connection strength *C* between two cortical areas. The parametrized MFM picks *w* and *G* values which maximize the statistical similarity between observed and simulated functional connectivity patterns across the entire brain. Multiscale models of cortical gradients similarly use macroscale data patterns to parametrize MFM values across the entire brain (see Section 3.1).

Deco et al. (2013) also used homogenized descriptions to determine what mesoscale features the macroscale functional connectivity patterns refer to. By using the inter-areal mean and interareal covariance of *S*, the MFM homogenizes a full spiking model that describes neural activity in a cortical area as the sum of synaptic activity of excitatory and inhibitory populations. In multiscale modeling in physics, homogenization has proven more successful than microscale averaging to explain how a collection of heterogeneous lower-scale behaviors contribute to macroscale behavior (Batterman, 2013). In the physics case, mean and covariance are used to *upscale* a lower-scale model because they describe how interacting lower-scale entities behave collectively. The MFM also uses covariance to describe how mesoscale circuit dynamics vary in relation to activity in other areas. But covariance alone cannot be used to upscale the MFM: *S* values cannot to be directly compared to macroscale functional connectivity patterns, which are calculated from BOLD values. So, to upscale *S* values, researchers use the Balloon-Windkessel model. Instead of upscaling the spiking model, the homogenization of *S* allows the researchers to “explore the parameter space of the model” (Deco et al., 2013, p. 11247), i.e. to find *G* and *w* values that fit the observed functional connectivity pattern. For these researchers, homogenization is “essential because it allows a thorough investigation of the brain system and a more exhaustive optimization of multiple parameters” (Deco et al., 2013, p. 11248). Based on the homogenized S values, they discovered that the parametrized *G* and *w* values lie close to a critical point where the low activity state of the network becomes unstable and switches to higher activity states. Critical behavior is relevant for many different brain functions because it could help us understand the brain’s ability to switch from resting state to various task-specific patterns of functional connectivity (Deco et al., 2013, p. 11250). And information about critical behavior was discovered by determining that resting state functional connectivity patterns (in part) refer to a feature of mesoscale circuit architecture—recurrent excitatory strength encoded by *w*. Homogenization can thus help researchers understand what mesoscale features their macroscale data patterns refer to.

The analysis of parametrization and reference determination completes the transposition of the multiscale modeling framework to connectomics (Table 1). According to this framework, information about the mesoscale is crucial if researchers want to use macroscale data patterns appropriately to parametrize models of circuit architecture, and if they want to homogenize microscale details to determine what features of brain organization the macroscale data patterns refer to.

The evidential role of mesoscale information for multiscale modeling suggests that inferences which directly link micro- and macroscale gradients can be problematic if they ignore mesoscale organization that realizes the structure-function relationship under study. Consider again Paquola et al. (2019), who infer from the divergence of micro- and macroscale gradients in transmodal association areas that “reduced hierarchical constraints enable functional diversity and flexibility” (Paquola et al., 2019, p. 14). This inference about the hierarchical structure-function relations in different parts of the brain is based on scale-specific modeling assumptions which link three gradient measures to features of cortical organization. First, microscale $\mathrm{G}_{\mathrm{HIST}}$ is linked to cytoarchitectonic similarity which predicts similar connectivity between areas (structural model). Based on this assumption, the divergence of $\mathrm{G}_{\mathrm{FUNC}}$ from $\mathrm{G}_{\mathrm{HIST}}$ supports the idea that transmodal association areas have diverse connectivity profiles, allowing them to integrate and broadcast different information types (Buckner and Krienen, 2013). Second, $\mathrm{G}_{\mathrm{MRI}}$, which is based on $\mathrm{T1}_{\mathrm{w}}/\mathrm{T2}_{\mathrm{w}}$ MRI maps, is linked to “increasing mean myelin content as well as a gradual transition in the relative myelin content around the midsurface” (Paquola et al., 2019, p. 8). This assumption can be taken to support the claim that “diverse connectivity profiles in transmodal cortices are likely related to heightened synaptic plasticity (García-Cabezas et al., 2017) that enables more flexible reconfigurations of functional relationships” (Paquola et al., 2019, p. 13). According to García-Cabezas et al. (2017) various molecular markers inhibiting synaptic plasticity, including intracortical myelin, are reduced in select prefrontal areas. Therefore, lower $\mathrm{G}_{\mathrm{MRI}}$ values at the transmodal end of $\mathrm{G}_{\mathrm{FUNC}}$ imply that transmodal association areas have lower mean myelin content than primary sensory areas, which enhances synaptic plasticity. Because Paquola et al.’s study does not use a mesoscale circuit model, it links $\mathrm{G}_{\mathrm{FUNC}}$ directly to *microscale* features (myeloarchitectonic and cytoarchitectonic similarity). Such direct linking is not itself problematic if microscale features can be used to correctly infer how a system realizes a structure-function relation like cortical hierarchy. It is, however, problematic if this relationship does depend on mesoscale organization which cannot be detected by simple averaging of microscale details (Batterman and Green 2020). This is exactly what the use of homogenization in multiscale modeling of Deco et al. (2013) showed: that functional connectivity patterns—the basis of $\mathrm{G}_{\mathrm{FUNC}}$—are also related to recurrent excitation strength *w*, which is a *mesoscale* parameter. Thus, the validity of inferences involving $\mathrm{G}_{\mathrm{FUNC}}$ also depends on the relation between mesoscale circuit features and aspects of hierarchical information processing such as flexibility. To describe this relation adequately, neuroscientists should move beyond direct comparisons of micro- and macroscale gradients and model mesoscale organization explicitly when linking cortical gradients to hierarchical information processing.

3. The role of mesoscale circuits in multiscale modeling of cortical gradients

3.1. Mesoscale information in current multiscale gradient models

Multiscale gradient models often assume that scale-specific gradient measures track one and the same hierarchical gradient which runs along the same spatial trajectory through cortex (from primary sensory to association areas). The following analysis of the role of mesoscale information in these models suggests that contrary to this common assumption, scale-specific gradient measures seem to track multiple overlapping gradients. The reason is that macro- and microscale descriptions of cortical gradients vary with distinct features of mesoscale circuits. Each of these features forms a progression that terminates in a different part of the cortex and is related to a different aspect of hierarchical information processing.

Multiscale gradient models have hierarchical fundamental presuppositions, i.e. they assume that a set of feedforward, feedback, and lateral connections underlies a signal processing hierarchy of input-output relations (Felleman and van Essen, 1991; Burnston and Haueis, 2021). The subsequent analysis focuses on three aspects of hierarchy prominent in the gradient literature: representational abstraction, integration

Table 1
Different types of multiscale models.

	Multiscale modeling of brain organization	Multiscale modeling of physical behavior
Aim of multiscale modeling	Discovery of patterns in brain organization that are relevant to many different brain functions	Explanation of a particular behavior of the physical system
Feature determination	Fundamental presupposition determines features of brain organization realizing structure-function relationship	Macroscale physical behavior determines explanatorily relevant features of the system
Utility of scale-specific models	Scale-specific modeling assumptions link data types to feature of brain organization	Scale-specific mathematical equations to model dominant behavior
Utility of upper-scale information	Upper-scale values are used to parametrize lower-scale model across entire domain	Upper-scale boundary conditions are used to restrict lower-scale model domain
Utility of lower-scale information	Lower-scale information is homogenized to determine the referent of upper-scale data pattern	Lower-scale information is homogenized to explain upper-scale behavior

time and flexibility. Note, however, that the resulting labeling of gradients is tentative, since the precise meaning of notions such as representation is debated in neuroscience and philosophy (Villarroya, 2017; Shea, 2018). The first aspect, *representational abstraction*, can be defined by (i) distance from sensory input and (ii) content heterogeneity (Margulies et al., 2016). Regarding (i), unimodal sensory areas primarily interconnect via short-range connections, whereas heteromodal and transmodal association areas increasingly interconnect via long-range connections (Oligschläger et al., 2018). Regarding (ii), the connectivity of transmodal areas allows them to integrate multiple unimodal sensory representations into categorical and rule-based ones (Mesulam, 1998; Pandya et al., 2015). Second, *integration time* increases along the hierarchy: areas are longer active when they integrate information from multiple modalities (Murray et al., 2014). Third, *flexibility* increases along the processing hierarchy, either due to (a) increases in diverse connectivity or (b) increases in synaptic plasticity. Unlike traditional sensorimotor hierarchies that link specific sensory inputs to motor outputs, neocortical association areas connect to a diverse set of areas, which allows them to (a) flexibly route their informational outputs to support multiple kinds of cognitive or motor functions (Buckner and Krienen, 2013). Unlike primary sensory areas, some prefrontal areas also show markers for increased synaptic plasticity (García-Cabezas et al., 2017), which allows them to (b) adapt their activity patterns more strongly to momentary task demands (Duncan, 2010).

Multiscale models link cortical gradients to these particular aspects of hierarchical information processing. The first four models (Table 2 left) presuppose that the laminar pattern of connections determines an area's position in the hierarchy. These models identify features of cortical organization which underlie a gradient of increasing *integration time* from primary sensory to prefrontal cortex (Chaudhuri et al., 2015, Burt et al., 2018, Fulcher et al., 2019). The last three models in Table 2 presuppose a sensory-fugal network gradient which terminates in a distributed set of neocortical association areas. The models link this gradient either to increased flexibility (Paquola et al., 2019 see Section 2.2), representational abstraction (Wang et al., 2019), or integration time (Demirtaş et al., 2019).

Table 2 reveals two essentially different kinds of using multiscale information in multiscale gradient models. The first kind includes mesoscale information in a data-driven description of cortical organization, summarizing cortical properties at multiple scales. (Burt et al., 2018; Fulcher et al., 2019, and Paquola et al., 2019). This data-driven use links scale-specific features via *reference determination* (e.g., that macroscale gradient measures could refer to dendritic spine density or myelination). Additionally, these models use correlations with cytoarchitectonic types to support inferences about convergent (Fulcher et al., 2019) or divergent gradients (Paquola et al., 2019). As discussed in Section 2.2, these inferences are difficult to assess because the data-driven use provides no top-down modeling constraint to link these correlations to specific features of circuit architecture.

The second kind of using mesoscale information alleviates this issue because it provides a circuit model which can be parametrized with upper-scale data values. (Chaudhuri et al., 2015; Schmidt et al., 2018a, Wang et al., 2019, Demirtaş et al., 2019). To assess whether the model-based use reveals one unified or multiple overlapping gradients at multiple scales, consider how Wang et al. (2019) and Demirtaş et al. (2019) parametrize the MFM. Both studies parametrize recurrent excitation strength (parameter *w*) to maximize the statistical similarity with either empirical resting state functional connectivity patterns, or with $T1_w/T2_w$ values. Although both parametrizations produce a mesoscale gradient of *w* values from primary sensory to neocortical association areas, they produce *opposing* results: in Wang et al. (2019, Fig. 2) *w* values are lowest for transmodal association networks, whereas in Demirtaş et al. (2019, Fig. 2), *w* values are highest in these areas.[3] The discrepant values are a robust result because parametrizations use different optimization procedures but both produce a better fit of simulated and empirical RSFC than the parametrization with homogenous *w* values (Deco et al., 2013).

Assuming that the discrepant *w* values are no methodological artefact, the multiscale framework suggests that they indicate multiple overlapping gradients. Demirtaş and Wang et al. use scale-specific assumptions to link the parametrized *w* values to different circuit features and aspects of hierarchical information processing. Demirtaş et al. (2019) link their parametrization to integration time because they assume that increasing *w* values refer to increases in dendritic spine density of layer 3 pyramidal neurons. They follow Burt et al. (2018) who infer from anatomical and genetic data that low $T1_w/T2_w$ values provide a homogenized description of increased recurrent excitation in cortical association areas. This increase is mediated by higher hhigehr higher dendritic spine densities of layer 3 pyramidal neurons. Since higher spine density allows these neurons to receive more excitatory synaptic inputs, it "may endow cortical circuits in association cortex with extended temporal integration" in comparison to primary sensory areas (Burt et al., 2018, p. 1253). By justifying high *w* values with this reference determination, Demirtaş et al. (2019) link their parametrization to *integration time* along the information processing hierarchy.

In contrast, Wang et al. (2019) link their parametrization to *representational abstraction* because they assume that increasing *w* values are linked to content heterogeneity, while decreases in subcortical input *I* are linked to distance from sensory input. The parametrized MFM model produces the highest *I* values in primary sensory areas and the lowest ones in the default mode network (DMN). Consequently, strong subcortical input to sensorimotor networks "might correspond to the flow of sensory information from the external environment via subcortical relays", whereas weak subcortical input suggests that the DMN lacks "a direct flow of information from the external milieu" (Wang et al., 2019, p. 7). Conversely, strong recurrent excitation could support "specialized local processing", such as the unimodal representation of stimulus features. By contrast, "weak recurrent connections might be consistent with the default network's putative role as a hub of transmodal information

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[3] To simplify the discussion, I speak of *w* values in both models, although the Demirtaş model parametrizes excitatory-to-excitatory and excitatory-to-inhibitory connections separately. Both parameters increase towards neocortical association areas.

Table 2

Comparison of multiscale modeling studies of cortical gradients. *Legend:* ∼ correlation, CMC: Canonical microcircuit, G_{FUNC}: principal gradient of functional connectivity, SC: Structural connectivity, RSFC: Resting state functional connectivity, $T1_w/T2_w$: weighted longitudinal over weighted transverse relaxation time, MFM: mean dynamic field model, *w:* recurrent excitatory strength.

	Chaudhuri et al. (2015) *macaque*	Schmidt et al. (2018a) *macaque*	Burt et al. (2018) *human/macaque*	Fulcher et al. (2019) *mouse*	Paquola et al. (2019) *human*	Wang et al. (2019) *human*	Demirtaş et al. (2019) *human*
Fundamental presupposition	Supra-granular projections determine hierarchy	Architectural types determine hierarchy	Multiscale gradient of hierarchical integration	Multiscale gradient of hierarchical integration	Sensory-fugal gradient of hierarchy	Sensory-fugal gradient of hierarchy	Sensory-fugal gradient of hierarchy
Macroscale modeling	29×29 SC matrix Simulated RSFC	32×32 SC matrix Network community structure	$T1_w/T2_w$	$T1_w/T2_w$	G_{FUNC} G_{MRI} (= $T1_w/T2_w$)	Empirical RSFC G_{FUNC} $T1_w/T2_w$ map	Empirical RSFC $T1_w/T2_w$ diffusion MRI SC
Mesoscale modeling	CMC	CMC, laminar connectivity, architectural types	cytoarchitectural types	cytoarchitectural types, cell type composition	cytoarchitectural types	MFM with gradient of w (primary sensory to DMN)	MFM with gradient of w (primary sensory to DMN)
Microscale modeling	Spine density gradient (primary visual to prefrontal cortex)	Gradient of indegree Areal neuron density + number	Gradient of gene expression (cell type, layers)	Gradient of gene expression (receptors, cell type, myelin)	G_{HIST} (primary sensory to paralimbic)	*none*	$T1_w/T2_w$ ~ spine density gradient
Parametrization	Scale excitatory inputs with position in hierarchy	Architectural type to fit connection + cell densities	*None*	*none*	*none*	Empirical RSFC to fit w and I	$T1_w/T2_w$ to fit w and G
Reference determination	Spine density gradient reduces FC ~ SC	Layer 4 neurons receive feedback signals	$T1_w/T2_w$ ~ spine density gradient $T1_w/T2_w$ ~ NMDA subunit	$T1_w/T2_w$ ~ in-degree $T1_w/T2_w$ ~ cell type density	$T1_w/T2_w$ ~ G_{HIST}	$T1_w/T2_w$ ~ w w & I distinguish primary & transmodal areas	Parametrized w increases simulated FC fit

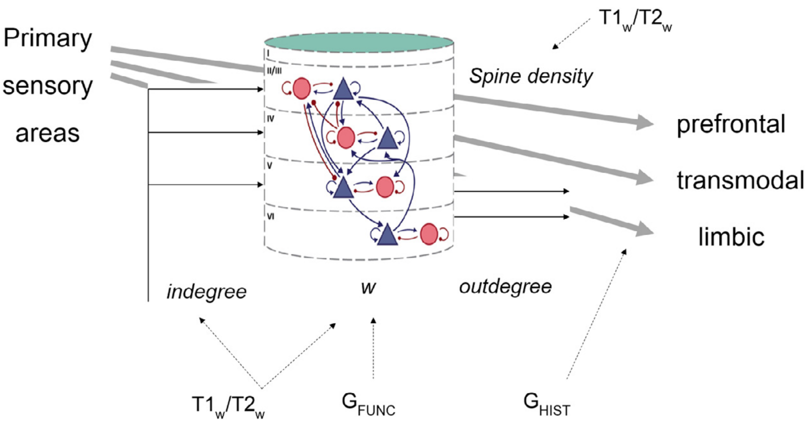

Fig. 2. Multiple overlapping gradients track different mesoscale circuit features. For acronyms, see legend of table 2.

integration” (Wang et al., 2019, p. 8). Thus Wang et al. justify low *w* values by linking their parametrization to representational abstraction.

The example of conflicting *w* values provides two reasons why current multiscale modeling studies may describe mesoscale circuits with multiple overlapping gradients. On the one hand, the two parametrizations reveal that *w* parameter MFM lumps different circuit features together (dendritic spine density, myelin and intracortical connectivity strength). On the other hand, the fact that opposing *w* values are linked to different aspects of hierarchical information processing suggests that macroscale gradient measures correlate with different features lumped in the *w* parameter. Such macroscale gradient measures thus seem to track multiple overlapping gradients which link mesoscale circuit features to different aspects of hierarchical information processing.

Fig. 2 visualizes the relations between three gradient measures and mesoscale circuit features. First, $T1_w/T2_w$ maps are related to dendritic spine density (Burt et al., 2018) and indegree (Fulcher et al., 2019), which are linked to increasing integration time. Second, macroscale G_{FUNC} seems related to a circuit feature linked to representational abstraction. Interlaminar circuit connectivity is one candidate (Section 3.2), but current gradient models already imply that the feature is not identical to dendritic spine density. DMN regions such as posterior cingulate and tempoparietal cortex have high degrees of abstraction (Margulies et al., 2016) but exhibit heterogeneous dendritic spine densities (Elston et al., 2005). Third, the microscale measure G_{HIST} detects cytoarchitectonic similarity, which is linked to flexibility. If flexibility means that a brain part supports multiple types of cognitive/motor functions via diverse, noncanonical connectivity profiles (Buckner and Krienen, 2013), then flexibility and representational abstraction have convergent endpoints in neocortical association areas. By contrast, if flexibility means how quickly a brain part reconfigures activity and connection patterns in response to momentary task demands, then flexibility and representational abstraction may diverge. In both cases, however, flexibility does not coincide with the endpoint of $T1_w/T2_w$ maps and dendritic spine density in the prefrontal cortex. Therefore, the different scale-specific measures may not characterize one overarching multiscale hierarchical gradient, but instead refer to multiple overlapping gradients in the cortex.

3.2. *Proposal for a mesoscale connectivity gradient*

Although multiscale gradient models already use mesoscale information, current approaches conceal circuit details that are relevant to assess inferences from gradient descriptions to hierarchical organization. Multiscale models using the MFM lump together circuit features that underlie inferences to different aspects of hierarchical processing (integration time, representational abstraction). Approaches using the CMC often assume that intrinsic circuit connectivity is qualitatively similar across areas (Chaudhuri et al., 2015; Schmidt et al., 2018a), which idealizes away circuit differences in granular, dysgranular and agranular cortices (Beul and Hilgetag, 2015). Moreover, none of the existing gradient measures explicitly characterizes how outdegree of mesoscale circuits varies between cortical areas. In this section I propose a qualitative model of a mesoscale gradient which includes these features and which sheds a new light on macroscale gradients. This gradient synthesizes and extends the work from the Hilgetag group by combining granularity-based differences in circuit architecture (Beul and Hilgetag 2015) with the architectonic type principle (Hilgetag et al., 2019). Granularity-based modeling differs from microscale modeling because it includes layer-specific cell types and their connections, and not just microscale properties of individual neurons (cell size, density). It also differs from macroscale modeling because it adds laminar origin to descriptions of interareal (extrinsic) connectivity patterns. Cell-type and layer-specific connectivity patterns underlie regular behaviors distinct from microscale neuronal or macroscale network activity, such as layer-specific oscillations (Bastos et al., 2015). The mesoscale gradient captures these facts in the fundamental presupposition that architectonic type membership determines the layout of extrinsic connections which underlie hierarchical message passing (Schmidt et al., 2018a,b).

Similar to micro- and macroscale gradients, primary sensory areas V1 and A1 lie at the beginning of the mesoscale gradient. These areas are clear cases of granular cortex: they have a high number of granule cells and a highly differentiated layer 4; overall cell density is high whereas soma size is small. Both excitatory and inhibitory connections exist between infra- and supragranular layers (Fig. 3C, circuit diagram I). The gradient proceeds to mostly granular areas such as primary somatosensory area and rostrolateral prefrontal areas, which have a clearly differentiated layer 4 but less overall and granule cell density (Ongür et al., 2003). Mostly granular circuits lack inhibitory connections between infra- and supragranular layers (Fig. 3C, circuit diagram II). Next are dysgranular areas such as the posterior DMN regions and lateral orbital and ventromedial prefrontal areas. In lack of anatomical data, the gradient postulates similar intrinsic connectivity as for mostly granular areas, while incorporating further decreases in neuron density paralleled by increases in soma size and dendrite numbers (Fig. 3C, circuit diagram III). Finally, the gradient terminates in agranular areas such as primary motor cortex and paralimbic areas (Fig. 3A, left). In agranular circuits, soma size and dendrite density are highest while neuron density is lowest, and inhibitory connections between layers are absent (Fig. 3C, circuit diagram IV). Assuming that synapse volume density remains constant, the concomitant increase in dendrites and decrease in neuron density means that the average indegree is increasing along the gradient (Schmidt et al., 2018a,b). Assuming intrinsic similarities between mostly granular and dysgranular areas, the average outdegree is higher in the middle of the gradient than at the ends because areas send out more local than long-distance connections.

The mesoscale gradient combines transitions from granular to agranular cortex with extrinsic, layer-specific connectivity (Schmidt et al., 2018a,b). High-to-low type (‘feedforward’) connectivity is dominated by supragranular projections whereas low-to-high type (‘feedback’) connectivity is dominated by projections to infragranular layers (Fig 3B, left and right). Horizontal connectivity shares features of both patterns (Fig. 3B middle). The mesoscale gradient relates these extrinsic connectivity patterns to granularity-based differences in circuit architecture. For example, L2/3 pyramidal neurons in dysgranular circuits connect to agranular excitatory and inhibitory L5/6 populations because agranular circuits lack L4 neurons. Moreover, granular and mostly granular circuits have similar feedforward connectivity patterns, whereas agranular and mostly granular circuits have similar feedback connectivity patterns.

Before using the mesoscale gradient to assess inferences linking micro- and macroscale gradients, we need to know the limitations of this model. First, despite discrete categories in Fig. 3A and C, the gradient characterizes both stepwise and continuous transitions from granular to agranular circuits. In many cases shifts between architectonic types are sharp and run along macroscopic brain boundaries (e.g. the granular-to-agranular shift along the central sulcus, Fig. 3A, left). In other cases, however, there are gradual transitions between architectonic types, such as the progression from agranular to granular areas in the dorsal paralimbic cortex (Sanides 1962, p. 107, Pandya et al., 2015, p. 297).

Second, the biological realism of the CMC model is debated since it is based on statistical analyses and not dense connectomic reconstructions (da Costa and Martin 2013). Although the mesoscale gradient is itself an abstract description, it increases the biological realism because it incorporates granularity-based connectivity differences neglected by previous gradient models. Thus, the use of the CMC in the mesoscale gradient follows a ‘middle out strategy’ that includes bottom-up details while simultaneously using top-down constraints to maintain generality, which is a strength of mesoscale modeling (da Costa and Martin 2013, p. 27, Batterman and Green 2020).

Third, some experiments suggest that motor cortex may not be agranular, since it has layer 4-like neurons which receive strong thalamic input and have feedforward excitatory projections (Yamawaki et al., 2014). Note, however, that unlike traditional accounts of layer 4 (Felleman and Van Essen, 1991; Douglas and Martin, 1992), the mesoscale gradient follows recent multiscale models which reveal that layer 4 receives substantial feedback connections, and that inhibitory connections dominate excitatory ones in simulations of spontaneous granular circuit activity (Schmidt et al., 2018a,b). Further research is needed to address how these novel insights affect the debate about agranular motor cortex. Yet the conclusions drawn below are somewhat independent from this debate because they are based on granularity differences between prefrontal and paralimbic areas rather than motor cortex.

Fourth, using the gradient in Fig. 3C as a description of *human* mesoscale architecture assumes anatomical similarities between human, nonhuman primate and rodent brains. For example: laminar connectivity patterns (Fig. 3B) are derived from macaque visual cortex (Schmidt et al., 2018a), and the circuit architecture for agranular and dysgranular CMCs (Fig. 3C) is drawn from studies in rodent cortex (Beul and Hilgetag, 2015). If further research discovers relevant interspecies differences for these mesoscale features, Fig. 3C should be revised accordingly. Yet the mesoscale gradient follows other connectomics models and assumes that connectivity patterns and circuit architecture are to some extent prototypical or canonical across a broader class of systems and species (Douglas and Martin, 1992; Ankeny, 2000; Haueis and Slaby, 2017; Goulas et al., 2018).

Despite its limitations, the mesoscale gradient provides a novel perspective on multi-scale modeling of cortical gradients. First, return to Paquola et al. (2019), who found that G_{HIST} and G_{MRI} run from primary sensory to paralimbic areas, rather than neocortical association areas. G_{HIST} and G_{MRI} thus parallel the mesoscale gradient, because primary

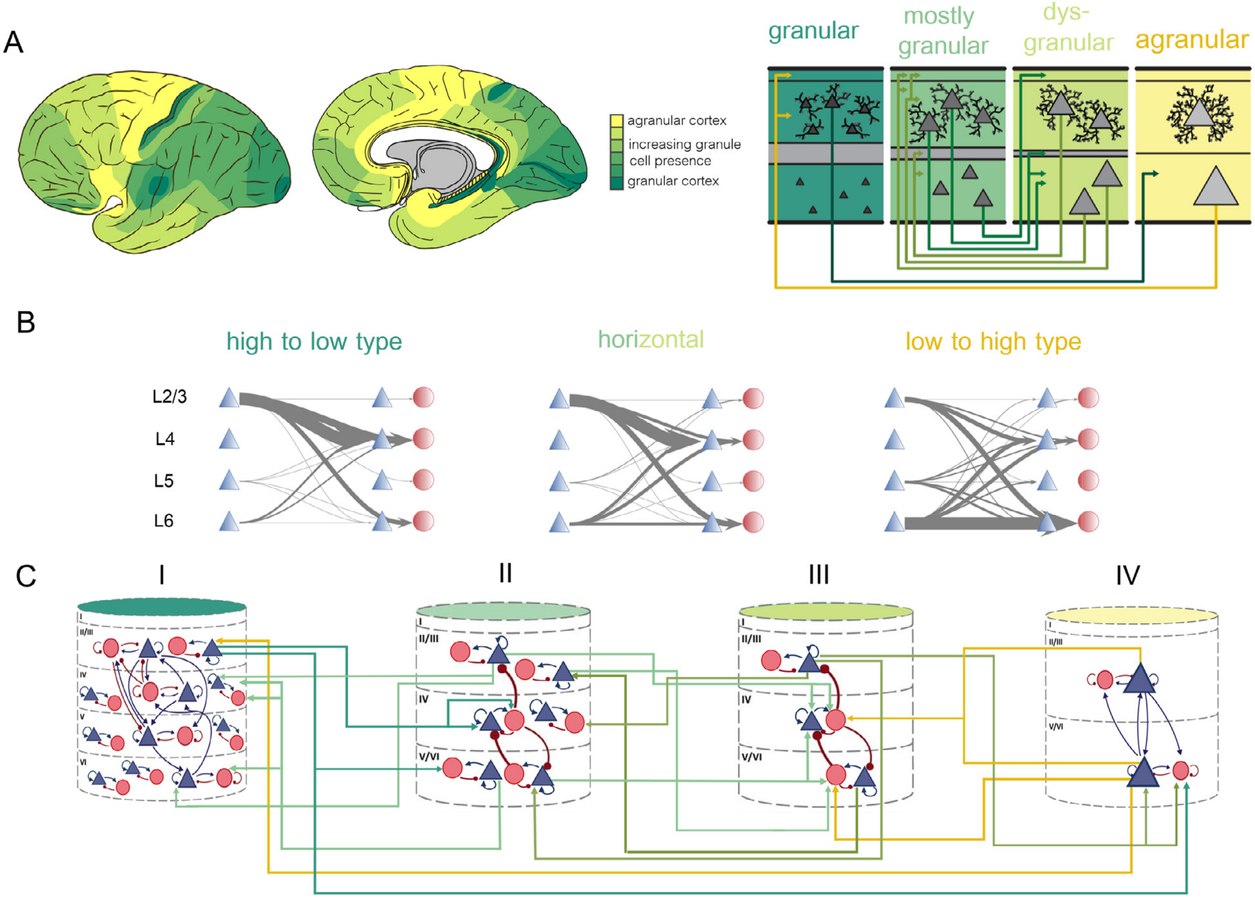

Fig. 3. (A) *Left:* distribution of granule cells and layer 4 in human cortex (lateral view adapted from Beul and Hilgetag (2015), anterior insula recoded as agranular; medial view based on von Economo (2009), Fig. 7. *Right:* Architectonic types defined by cell density, soma size, dendrite density and granularity. Connections between different architectonic types vary in density and laminar origin (Hilgetag et al., 2019). (B) Cell-type specific interlaminar connectivity between different architectonic types. High-to-low connections are predominantly supragranular, whereas low to high connections are predominantly infragranular. Horizontal connections show intermediate patterns (adapted from Schmidt et al., 2018b). (C) Mesoscale gradient of circuit connectivity links the cytoarchitectonic type principle and cell-type specific connection patterns to shifts in circuit architecture from granular to agranular areas (circuit diagrams modified from Beul and Hilgetag, 2015). . (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

sensory areas are granular while most paralimbic areas are agranular. Furthermore, low G_{HIST} values (indicating high cell density in granular layer 4) are located in primary sensory areas, and high G_{HIST} values (indicating low cell density in layer 4) are located in agranular paralimbic areas (Paquola et al., 2019; Fig. 2B and C). In humans, these areas are anterior insula, anterior cingulate area 32, prelimbic area 32, areas 24, 25 and area 14c (Ongür et al., 2003). The are also sparsely myelinated, which may explain why paralimbic G_{MRI} values are maximally distinct from values in primary sensory areas (Paquola et al., 2019. Fig, 3C and D).

This correspondence has three implications. First, Paquola's inference that the divergence of G_{FUNC} from G_{HIST} and G_{MRI} supports flexible processing runs together two features of cortical organization that form two distinct gradients. Paquola et al. relate increased flexibility both to (a) diverse connectivity profiles and (b) enhanced synaptic plasticity in the default mode and fronto-parietal network. With regard to (a) it is true that diverse connectivity profiles (divergence of G_{FUNC} from G_{HIST}) allow these networks to integrate multiple types of information and broadcast the resulting representations to support multiple cognitive functions. This notion of flexibility is roughly equivalent to content heterogeneity, and therefore linked to representational abstraction (Margulies et al., 2016). Regarding (b), however, both networks do not have the highest synaptic plasticity, even though they are more plastic than primary sensory regions. For example: the frontoparietal and default mode network consists of areas in the rostrolateral and medial frontal gyrus. Their homolog macaque areas 9/46d and area 10m are mostly granular and have increased molecular markers for inhibiting synaptic plasticity (García-Cabezas et al., 2017, Figs. 2–4). By contrast, paralimbic prefrontal areas 25 and 32 exhibit increased molecular markers for enhanced synaptic plasticity Garcia-Cabezas et al. 2017, Figs, 5–6). This means that paralimbic circuits at the endpoint of G_{HIST} and the mesoscale gradient are more flexible to plastically change their synaptic connectivity than prefrontal areas in the frontoparietal and default mode network.

Second, the correspondence of G_{HIST} and the mesoscale gradient implies that cortical gradients for integration time, flexibility and representational abstraction only overlap in some but not other parts of neocortex. Multiscale gradient models commonly assume that these aspects are inseparable components of the same hierarchical processing gradient (Elston, 2003; Fulcher et al., 2019). In contrast, the mesoscale gradient suggests that whereas dendritic spine density and integration time are highest in agranular circuits such as anterior cingulate cortex (Elston et al., 2005), these circuits have lower degrees of representational abstraction than transmodal association cicruits. Agranular paralimbic areas connect to a diverse set of multimodal and prefrontal areas which allows them to represent heterogenous contents (Lavenex and Amaral 2000; Pandya et al., 2015, ch. 11). But these areas have reduced distance to sensory inputs because they are strongly connected to olfactory, gustatory, somatosensory cortex and the amygdala. Based on these inputs, agranular paralimbic circuits contribute to visceral functions, the processing of olfactory and gustatory information, pain perception, as well as linking mood to cognition (Pandya et al., 2015, p. 315). This functional profile of the agranular end of G_{HIST} and the mesoscale gradient is in sharp contrast to the transmodal end of G_{FUNC}, where activity correlates with functions such as social cognition, verbal semantics, autobiographical memory and internal mentation more generally (Margulies et al., 2016; Wang et al., 2019).

Third, the granularity-based differences (Fig. 3A) imply that neocortical association areas at the end of G_{FUNC} are situated in the middle of the mesoscale gradient. For example, posterior components of the DMN predominantly belong to the dysgranular type: although laminar differentiation varies, most areas of posterior cingulate cortex have a dysgranular layer 4 (Vogt et al., 1995). Precuneus similarly has a small but differentiated layer 4 (Scheperjans et al., 2008). Prefrontal DMN regions like orbitofrontal and medial prefrontal cortex are composed of mostly granular and dysgranular circuits (Ongür et al., 2003). This suggests that high levels of representational abstraction in DMN areas may be supported by *heterogenous* connectivity patterns at the mesoscale of cortical circuits, even though this network exhibits homogenous functional connectivity patterns at the macroscale.

The mesoscale gradient can furthermore help answer why DMN regions display low *w* values in Wang et al.'s (2019) parametrization of the MFM. Because dysgranular circuits possess interlaminar inhibitory connections whereas agranular ones do not, recurrent excitation should be weaker in these circuits than in agranular ones. Wang et al.'s results support this interpretation at least in part because *w* values in paralimbic areas are higher than in neocortical association areas, although not as large as in primary sensory and motor cortex (Wang et al., 2019, -Fig. 2A). The mesoscale gradient thus helps to determine exactly which circuit features—dendritic spine density and interlaminar inhibition—were lumped together in the *w* parameter of the MFM. Distinguishing these features with separate modeling parameters helps us appreciate that increased excitatory input is not the only feature relevant to representational abstraction. Interlaminar inhibition also seems to contribute to the integration of various types of informational input in neocortical association networks.

Besides distinguishing circuit features via reference determination, researchers can also parametrize the mesoscale gradient with macroscale functional connectivity values. For example: one end of the second gradient of functional connectivity (Fig. 1B, top) summarizes over mostly granular somatosensory and agranular motor cortex. Multiscale studies could inquire whether these areas have similar macroscale connectivity patterns because mostly granular and agranular circuits share similar interlaminar feedback patterns (Fig. 3C). The mesoscale gradient thus can help multiscale modeling to summarize similar circuit features in the same parameter and distinguish dissimilar features in different ones

Conclusion

This paper argued that the mesoscale of cortical circuits is crucial to link micro- and macroscale models to different aspects of hierarchical information processing. To assess inferences in the gradient literature, I transposed the framework of multiscale modeling from physics to neuroscience. Going beyond existing philosophical accounts of multiscale modeling (Wilson, 2017; Green and Batterman, 2017 Batterman and Green 2020), the transposition showed multiscale models of cortical gradients do not aim at explaining a particular type of behavior but to discover patterns of brain organization which are relevant to many different types of neural functions. Multiscale models in physics use boundary conditions and homogenization to restrict the model domain and select explanatorily relevant information. Connectomic multiscale models use parametrization and reference determination to explore the entire lower-scale model domain and to assess what features of cortical organization are represented by upper-scale data values. The multiscale framework therefore advances the field of connectomics by highlighting which tools connectomics researchers can use for "understanding, specifically, how network properties at one spatial scale are related to properties at another" (Betzel and Bassett, 2017, p. 80).

I used the framework to analyze the role of mesoscale information in multiscale models of cortical gradients, which frequently assume that different features of cortical organization are organized into one and the same cortical gradient of hierarchical information processing (Burt et al., 2018; Fulcher et al., 2019). My analysis shows instead that gradient measures are related to different circuit features such as indegree or recurrent excitatory strength, or interlaminar inhibition. This result supports the view that cortex is organized into multiple overlapping gradients (von Bonin and Bailey 1951; Paquola et al., 2020). The present analysis tentatively labelled these gradients in terms of representational abstraction, integration time and flexibility. While gradients for different aspects of hierarchical information processing coincide in occipital cortex (cf. Hilgetag and Goulas, 2020, p. 8) they diverge towards different spatial endpoints in prefrontal cortex. There, the gradient concept describes both agranular paralimbic circuits, which are an interface for interoceptive and exteroceptive information with high synaptic flexibility and low distance to sensory inputs; and the default mode and frontoparietal networks, which have a high distance to sensory input but lower synaptic flexibility.

Whereas this paper focused on the role of mesoscale anatomy and physiology in multiscale gradient models, further research should explore how gradients of hierarchical information processing are related to the computational, dynamic and topological organization of the brain. Computational models could use the mesoscale gradient to explain how interlaminar inhibition contributes to the transformation of multiple information types in an abstract representation. In a predictive coding framework, for instance, interlaminar inhibition of supragranular neurons minimizes updating of expectations by lower-level prediction errors (Bastos et al., 2012). To explain how a specific circuit creates an abstract representation, researchers need to add area-specific incoming connections to this computational model, because they over which types of information the circuit computes a prediction. Multiscale models are also helpful to study dynamic features because they relate them to distinct connectivity measure. For example, Schmidt et al. (2018a, p. 11244 p. 1424) show that synaptic indegree is related to time-averaged spike rates whereas interareal connection probabilities are related to the correlation of time series. Here, mesoscale information is crucial: modeling layer-specific indegrees is necessary to link microscale studies of cortical dynamics, which measure spike rates, and macroscale studies of functional connectivity dynamics, which measure correlations. The relation to degrees of connection furthermore points towards the importance of topological organization for understanding dynamics along cortical gradients. Topological analyses of hierarchy focus on the ability of a part of the brain to integrate, broadcast, or gate information, but are neutral with respect to representational abstraction (Burnston and Haueis, 2021). Future multiscale studies could use graph-theoretical tools to analyze in- and outdegrees along different parts of the gradient of representational abstraction to explicitly explore the relation between representational and topological hierarchies.

Credit author statement

Philipp Haueis conceptualized, wrote and revised the original article.

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