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Review

Autism-related shifts in the brain's information processing hierarchy

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Despite considerable research efforts, mechanisms of autism remain incompletely understood. Key challenges in conceptualizing and managing autism include its diverse behavioral and cognitive phenotypes, a lack of reliable biomarkers, and the absence of a framework for integration. This review proposes that alterations in sensory-transmodal brain hierarchy are a system-level mechanism of atypical information processing in autism. Hierarchies can account for diverse autism symptomatology and help explain common neurodevelopmental hallmarks, notably a shift away from socially biased information processing, and an enhanced role, autonomy, and performance of perception. A hierarchical reference frame can also subsume spatially heterogeneous neuroimaging findings and make conceptual contact with foundational theories of cortical information processing, thereby consolidating behavioral, cognitive, computational, and neural characteristics of the condition.

Highlights

Cognition can be described as a sequence from sensory/perceptual processing toward integrative, transmodal, and sociocognitive operations, which is mirrored in macroscale cortical hierarchical organization.

The diverse behavioral phenotype of autism can be described in terms of imbalances in these hierarchies, in particular in a shift from social toward nonsocial information-processing bias.

Increasing findings from neuroimaging and connectomics research suggest an atypical organization of brain network hierarchies in autism at both the structural and functional levels.

By adopting a system-level perspective on neural information processing, a hierarchical reference frame can consolidate seemingly inconsistent and regionally heterogeneous findings in autism.

Hierarchical accounts may also help in bridging molecular, network, and behavioral facets of autism, thereby integrating micro- and macroscale mechanisms.

Understanding autism requires an umbrella framework

Autism is an early emerging, common, and lifelong neurodevelopmental variant [1]. Despite considerable research efforts, it remains poorly understood. Moreover, today's primary approaches to supporting people with autism build on educational, psychological, and parental support aimed at addressing specific needs [2] while respecting behavioral atypicalities and fostering specific strengths. Although such efforts are valuable for improving well-being and societal acceptance, they are generally not grounded in an understanding of biological mechanisms.

One challenge in diagnosing, understanding, and supporting individuals with autism lies in integrating variable sensory-perceptual alterations across individuals [3,4], alongside imbalanced verbal and nonverbal competencies [5–7] and atypical social-cognitive functions [8–10]. An overarching account of these alterations remains largely absent, because most frameworks have emphasized a specific cognitive function (e.g., perceptual alterations, deficits in 'Theory of Mind,' atypical predictive processes; see Box 1). An account focusing on information-processing hierarchies in the brain may help consolidate prior frameworks. This account could also connect behavioral studies with the growing body of neuroimaging and connectomics research showing atypical brain network organization and hierarchical spatial patterning in autism at both the functional and structural levels [11–14].

This review first provides a brief overview of cognitive processing hierarchies and how these are mirrored in the layout of macroscale neural systems. Evidence now consistently shows a hierarchical structure in the human brain at the levels of cortical microstructure, connectivity, and function (Box 2 [15–20]). These macroscale trends, also referred to as 'brain gradients,' generally extend from systems that interact with the external world through perceptual processing streams and attentional systems toward transmodal association networks involved in language, social-cognitive, and socioaffective functions [18,19,21,22]. Sensory-transmodal hierarchical axes can

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Box 1. Conceptualizations of autism

One prominent theory that highlights social cognitive deficits hypothesizes a specific association between autism and impaired 'Theory of Mind' [112,113]. More recent work describes autism instead via an enhanced role, autonomy, and performance of perception, which in later developmental stages cascades into alterations in higher systems as well and can thus account for social cognitive deficits alongside perceptual changes [62,64,114]. The marked increase in prevalence and recognized heterogeneity of autism have sparked debates about the interaction between diagnostic criteria, mechanistic explanations, the status of autism as a biological entity, and research study design.

One position considers autism as a natural category characterized by a marked discontinuity from the typical population that results from an abrupt and family-bounded bifurcation toward an absent social information-processing bias [98,115]. Autism would then pertain to the same family of embryologic and information-processing variants as left-handedness, twin pregnancy, and breech presentation: a human possibility, sometimes with marked adaptive consequences. A large part of the current heterogeneity of the spectrum would, in turn, originate from the increasingly broad phenotypic criteria used to diagnose autism and from the resultant variability of research cohorts. Consequently, the position recommends the targeted study of cohorts presenting with a strong, prototypical phenotype.

Alternatively, a continuum model considers autism as an intrinsically heterogeneous and dimensional condition, which culminates from the convergence of multiple dimensional mechanisms and traits [116]. This model overall sees value in a transdiagnostic approach that integrates research across multiple comorbid and neurodevelopmental populations and that generally orients toward population-level studies of a large number of individuals to adequately embrace clinical and subclinical traits.

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help us understand the spatiotemporal maturation of neural networks and their relation to milestones in sensory-perceptual, cognitive, social, and linguistic development in neurotypical individuals [22–26].

The review next focuses on how autism can be understood as a shift away from typical hierarchical information processing. It provides an overview of how this framework integrates prior theories and empirical evidence related to enhanced perceptual functioning, atypical predictive learning, and the absence of bias toward social cues. By framing autism in terms of atypical hierarchical information processing, we can better address the apparent diversity in autism symptomatology. This perspective is supported by brain imaging and connectomics studies that demonstrated atypical structural and functional hierarchies in autism. These studies suggest that using a hierarchical reference frame can enhance understanding of autism and its heterogeneity, particularly in relation to theories that view autism as a deviation from typical developmental paths [27]. Indeed, because hierarchical organizational accounts and hierarchical gradients, in particular, subtend the entirety of cortex, they could help explain a broad spectrum of autism-related behaviors, including sensory-perceptual, interoceptive, interpersonal, and linguistic phenotypes.

Box 2. Hierarchical organization and brain gradients

Foundational neuroanatomical work, theoretical considerations, and an increasing body of recent systems neuroscience work have collectively suggested a hierarchical organization of brain systems, where specific definitions of 'hierarchy' vary across studies [15,21,117,118]. One line of studies has emphasized the presence of macroscale spatial gradients of cortical organization in the human brain that emphasize a topological sequence of different regions/systems [17,19,20,41,42,119,120]. Such gradients have been pioneered at the level of functional neuroimaging [19], but they have also been largely recapitulated when studying (micro)structural neuroimaging as well as histological and gene expression information [18,42,121]. Although results can vary across modalities, approaches, and populations, a frequently described gradient runs in sensory-transmodal direction, compatible with a sensory-fugal neural processing hierarchy. It is important to emphasize that the contemporary focus on sensory-transmodal spatial trends does not preclude the possibility of other, potentially more fluid forms of brain network organization. In addition to emphasizing sensory-transmodal arrangements, prior research has also pointed to additional gradients, such as those differentiating visual versus somatomotor systems and those distinguishing multiple demand networks implicated in cognitive control [19,122]. This is in line with the dynamic nature of brain function, where multiple networks may interact in a context-dependent and complex way. As such, sensory-transmodal gradients may simply represent one common mode of multiple, hierarchically ordered configurations. Alternative and potentially more flexible configurations, including heterarchies [123], may therefore be an important avenue for future investigations.

This review closes by formulating open questions and challenges and by making recommendations for future work. An account centered on information-processing hierarchies in autism will help unravel the neural mechanisms of autism, clarify the association between system-level substrates and observable atypicalities, and enhance differential diagnosis and the potential discovery of relevant autism subtypes [28,29]. Ultimately, these efforts may help to identify biology-informed strategies that complement current behavioral interventions.

Information-processing hierarchies in typical development

Neurocognitive hierarchies

Cognition is organized in the brain in a hierarchical and bidirectional manner [30–32] anchored by the sensation of stimuli from the external environment on the one end and self-generated and internally oriented processes on the other end [21]. Incoming information is serially processed and modulated on the basis of attentional focus on specific aspects of that information. This information is temporarily held and manipulated at an intermediate level of perceptual integration. Higher up the hierarchy are integrative and increasingly self-generated processes in addition to control functions that monitor and adjust actions based on internal goals, expectations, and environmental demands [21]. In addition to this 'bottom-up' flow of sensory information along perceptual streams toward higher-order processing, 'top-down' feedback is equally present, shaping predictions of ongoing, lower-level information processing based on context, experience, and overall goals [20,33–35].

Early models of the cortical hierarchy were formulated on the basis of research conducted in non-human primates, which are now increasingly being extended to humans [20,21,31,32]. Hierarchical topography maps a progressive transformation of incoming sensory information into integrated neural representations (Figure 1A, [36,37]). This architecture provides a basis for the functional distinction between the processing of information from the immediate environment and of self-generated or internal operations that are decoupled from immediate sensory inputs. Such operations include cognitive perspective taking, simulative operations, inner language, emotional processing, and long-term planning [20]. As such, brain hierarchy organizes both the generation of high-level representations of the environment and predictions about it. This, in turn, influences sensing, perceiving, anticipating, and acting in dynamically changing contexts (often conceptualized as 'predictive coding' [38–40]).

Recent studies have applied data-driven techniques to high-dimensional functional neuroimaging datasets to identify spatial gradients in brain organization that recapitulate the putative information-processing hierarchy (Figure 1B, Box 2). These studies have converged on showing a principal gradient that follows a sensory-transmodal pattern [17,19,41]. The gradient radiates from sensory and motor systems that interact with the here and now toward transmodal associations systems such as the default mode network. The latter systems are increasingly implicated in integrative and higher-order cognitive processes that may or may not be perceptually decoupled. Other gradients (explaining additional variance in brain function) differentiate other macroscale systems, such as sensory/motor and visual systems that interact with the external environment (Figure 1C).

Notably, by offering a dimensional perspective on brain organization and by imposing a natural ordering of specific regions and systems with respect to these axes, gradient mapping techniques may help to establish a low dimensional coordinate system in which macroscale cortical organization can be understood, analyzed, and related to other features of neural organization and hierarchy (Figure 1D). Although exact results may vary, depending on input modalities, and overall convergence is indeed seen across *in vivo* functional connectivity during both resting and task contexts, MRI-derived indices of myeloarchitecture and microstructure, and data from

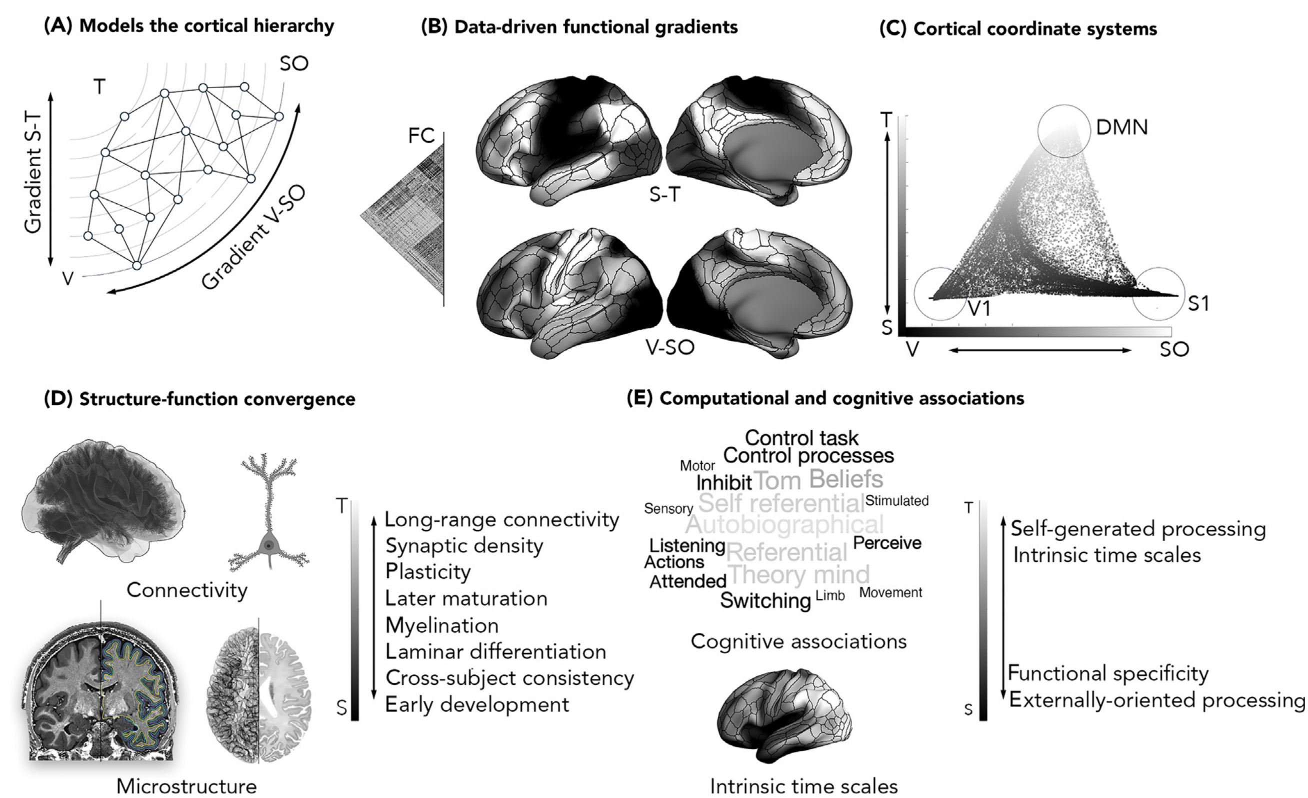

Figure 1. Cortical and cognitive hierarchies. (A) Foundational models of the primate cortical hierarchies describe a stepwise transition from sensory and motor systems interacting with the external environment [e.g., visual (V); somatosensory/motor (So)] and transmodal regions (T) that are increasingly implicated in self-generated processing [19,21]. Figure modified from [19]. (B) Nonlinear dimensionality reduction techniques can be applied to functional connectivity data in a fully unconstrained manner (here based on a subset of young adults from the human connectome project dataset, openly available at https://www.humanconnectome.org). The resulting components describe spatial gradients in brain function. A first component, explaining most variance, runs from sensory/motor systems toward transmodal systems such as the default mode network and thereby closely recapitulates the cortical hierarchy (S-T axis, sometimes also referred to as sensory-association axis). A second component differentiates visual from somatosensory/motor systems (V-So), providing a differentiation of externally oriented systems [19]. (C) It is possible to arrange cortical regions in a new coordinate system spanned by different gradients. In the example, regions are being organized according to S-T and V-So axes. Transmodal systems such as the default mode network cluster toward the top of the graph, whereas sensory and motor systems occupy bottom parts. Generated on the basis of the same data as (B). (D) Different structural features, including cortical microstructure and long-range connectivity, have been found to be, in part, organized along the S-T axis. (E) Similarly, the S-T axis has been found to relate to external-internal functional processes when participants undergo functional neuroimaging tasks as well as interareal differences in neural computational properties, such as intrinsic timescales.

postmortem histology and transcriptomics ([18,19,42]). Moreover, there is now mounting evidence that data-driven gradients also covary with other computational aspects of cortical hierarchical organization, including intrinsic time scales as well as externally versus internally oriented computation (Figure 1E).

Developmental perspectives

Throughout typical childhood development, specific cognitive functions generally mature in a staged manner that aligns with a sensory-transmodal information-processing hierarchy [22]. Information processing in newborns and toddlers appears to prioritize sensory-motor exploration. As development progresses, this is increasingly complemented by the maturation of linguistic interactions, socioemotional processing, and higher cognitive functions related to social and language-mediated cues [43,44]. Ultimately, those seem to be related to a progressive differentiation of relevant functional systems throughout development, in particular the increasing differentiation between systems mediating sensory/motor functions and networks implicated in higher-order transmodal functions.

These cognitive findings have been supported by neuroimaging studies that have explored the development of cortical structural and functional networks and that suggest a key role of sensory-transmodal axes in developmental staging [22,45]. At birth and shortly thereafter, hierarchical patterning is not fully matured, and the main axis of cortical function still runs primarily between somatomotor and visual systems [46]. This is consistent with functional gradient mapping results [46] and the mapping of highly connected structural and functional hubs in neonates [47,48], which still reside primarily in sensory and motor systems. In preschoolers aged from 4.5 to 6 years, recent studies have furthermore supported a relative stability of this pattern [49]. In later childhood and adolescence, the main axis of cortex-wide functional differentiation then shifts gradually toward the sensory-transmodal pattern that is also seen in adults [26]. Concerning the exact developmental timing, a recent study reported this shift toward the adult-like configuration occurs sometime between 12 and 14 years of age [26]. This emergence reflects an increasing maturation and functional differentiation of transmodal association systems, such as the default mode network, from sensory and motor systems, possibly through a relative strengthening of anterior-posterior structural and functional connections [25,50].

Although most of these findings have been described at the level of corticocortical connectivity, there are parallel subcortical-cortical connectivity changes that partially align with these reconfigurations. For instance, during typical development, there are changes in connectivity between the thalamus, basal ganglia, and neocortex, with some marked reconfigurations in the connectivity to transmodal regions [51]. A previous functional connectivity assessment, for instance, has suggested a marked role of thalamocortical functional connectivity changes in the strengthening of sensory-transmodal axes, particularly between 12 and 18 years of age [51]. Parallel studies assessing brain fiber tracts observed consistent maturational processes, pointing to microstructural changes across multiple white matter systems, mediating both corticocortical and subcorticocortical communication [18,52]. Developmental changes are seen across virtually all major tracts. Yet, the fiber bundles interconnecting distributed regions of transmodal systems, such as those in the default mode network, undergo some of the most marked changes during childhood and adolescence. These findings were recently contextualized along sensory-transmodal cortical gradients, which could reveal that thalamocortical structural connections mature at progressively older ages the more they connect to transmodal regions [53]. Similar developmental trajectories are apparent when assessing cortical microstructure, with myelination changes that also follow a sensory-transmodal pattern [52,54]. This ultimately reflects an increased microstructural differentiation between early maturing sensory/motor systems (that have overall higher myelination and more pronounced cortical lamination patterns) from transmodal association areas that mature late (and that have overall lower myelination and less demarcated lamination patterns). Functionally, sensory-transmodal differences in the timing of myelination of cortical areas may relate to their potential for plastic change, with transmodal areas showing experience-related plasticity at the functional and microstructural levels far into adulthood [55,56].

Despite the marked role of genetic factors in developmental programs, cortical and cognitive maturation is most influenced when a cortical region's peak plasticity period coincides with exposure to engaging experiences [22]. Early in life, sensory and language experiences disproportionately affect brain development, in particular in corresponding brain systems, whereas later deprivation of these stimuli has only minimal effects [57]. Cognitive, social, and emotional experiences continue to shape cortical development throughout childhood, adolescence, and early adulthood due to sustained plasticity in higher-order systems situated in transmodal association areas [55,58,59]. Cortical gradients, in particular those following sensory-transmodal axes, can help in the understanding of spatiotemporal patterns and relevant milestones both in typical development and in conditions associated with atypical brain network organization such as autism.

Autism as a condition of atypical information-processing hierarchies

Behavioral alterations

Autism has a multifaceted behavioral phenotype emphasized by the interplay of social signs (alteration of synchronous, reciprocal social interactions and their nonverbal counterparts and of long-term relations) and nonsocial, repetitive signs (intense interests, repetitive movements, resistance to change, and perception-based behaviors) [60,61]. Although the conceptualization and diagnosis of autism has undergone several transformations, approaches generally emphasize that some types of information are atypically processed (Figure 2A). In early cognitive models and clinical descriptions of autism, as well as in the most recent edition of the *Diagnostic and*

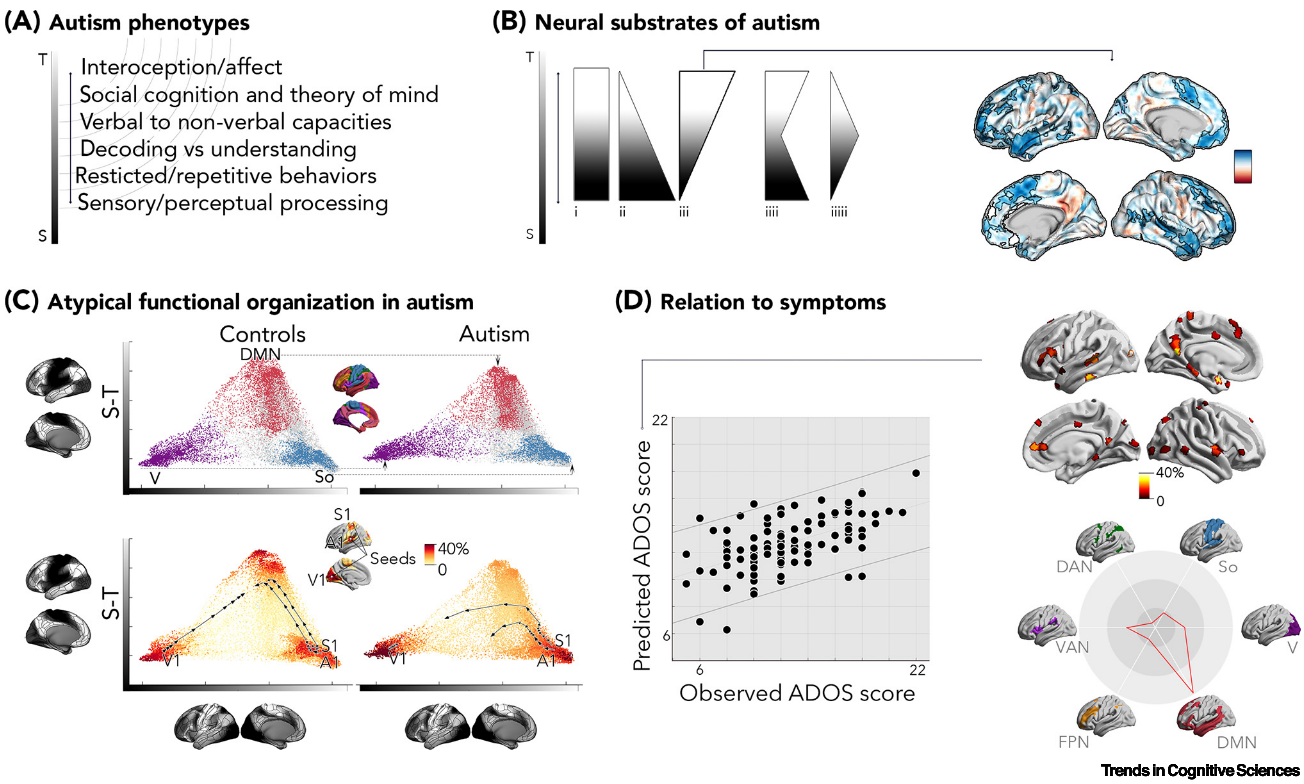

Figure 2. Hierarchical alterations in autism. (A) A broad range of behavioral phenotypes have been associated with autism, and these are thought to occupy different levels of cortical hierarchical processing. (B) Potential relationship between autism-related neural alterations and the cortical hierarchy: (i) All levels are similarly affected, (ii) increased effect in sensory/motor regions, (iii) increased effects in transmodal areas, (iiii) increased effects in sensory/motor and transmodal areas with relatively sparing of intermediary levels, (iiiii) increased effects in intermediary levels, with relative sparing of sensory/motor and transmodal regions. An exemplary study [102] that more closely fits into model (iii) is shown. Reproduced with permission via http://creativecommons.org/licenses/by-nc-nd/4.0/. (C) Atypical network topographies at macroscale in autism, showing overall and alteration of sensory-transmodal gradients [101]. Reproduced with permission via http://creativecommons.org/licenses/by-nc-nd/4.0/. Left top: Different regions in control individuals and individuals with autism represented in a 2D 'gradient space' (along an S-T and V-So axis). The findings show reduced distance in this space between sensory/motor and transmodal systems in autism. Left bottom: Stepwise functional connectivity (SFC) propagation analysis in the same 2D gradient space, showing an atypical SFC evolution in autism. In particular, although SFC patterns (depicted as black arrows in the gradient space) run from sensory systems toward the default mode network (DMN) in relatively straight lines in neurotypical individuals, SFC paths seem altered in autism and do not show a DMN convergence. (D) Hierarchical features have also been shown to help predict Autism Diagnostic Observation Schedule symptom severity in autism, and features seem to be selected across multiple networks, with DMN regions being most frequently selected [101]. Reproduced with permission via http://creativecommons.org/licenses/by-nc-nd/4.0/.

*Statistical Manual of Mental Disorders (*DSM) [62], sensory-based manifestations have become a key feature of autism [63]. Although altered sensitivity to sensory stimuli is not specific to autism, it is very common, and enhanced perceptual functioning appears to be prevalent in this population [64,65]. Altered perceptual processing and behaviors have been shown across a broad spectrum of sensory modalities [66], mostly vision [67], but also audition [3], somatosensation, and proprioception [68,69], as well as olfaction and gustation [70]. Several studies also suggest an increased prevalence of altered interoception and body awareness in autism [71–74], which can result in reduced well-being. Atypical information processing is exemplified in increased perceptual abilities observed in some autistic individuals in specific domains [75,76].

In addition, there is ample evidence of atypical multisensory integration in autism, which is consistent with a reorganization of higher-level transmodal functions [4,77]. Synesthesia and absolute pitch, extreme forms of this phenomenon, are about 100 times more prevalent in autistic individuals than in neurotypical individuals [78,79]. Furthermore, autistic people may demonstrate atypical attentional shifting and altered selective attentional mechanisms [80]. It has also been suggested that attentional resources are shifted toward a smaller number of interests in autism, which has been referred to as monotropism [81]. This may take place even before visible manifestations of autism, which could explain why many individuals with autism are overwhelmed by dynamic sensory environments [4]. Likewise, there is a higher occurrence of savant abilities in autism, which often involve focusing on and mastering nonsocial (e.g., objects, routines, sensory inputs, special interests, logical systems) patterns [82]. The latter may be linked to the brain's automatic ability to recognize patterns across different levels and scales [76].

The reorganization of sensory, attentional, and integrative functions may propagate into other domains of autism symptomatology, leading to reduced attentional bias toward sociocognitive information. In fact, some of the earliest and most striking aspects of autism are diminished overt and spontaneous attention to voices and faces. This shift, on the other hand, has been associated with increased attention to nonsocial aspects of the world. This occurs first gradually during the third semester, then becomes more pronounced during the fourth semester of life [83,84]. This could help explain the quasiabsence of typical cognitive perspective taking, which often becomes apparent during childhood and is critical for autism diagnosis in its most prototypical forms. Autism becomes most frequently visible during the fourth semester. During that period, overtly altered sensory and social behaviors may stem from a common underlying bifurcation that reverses typical social and nonsocial processing biases [85]. This moment corresponds to the lexical splurge in typical development. In autism, on the other hand, the limited vocabulary acquired so far may regress or plateau without considerable language progress, which may last up to several years. There is furthermore a higher discrepancy of nonverbal versus verbal skills in autism than in neurotypical individuals. An imbalance in verbal and nonverbal intelligence quotient [86,87] is consistent with many autistic individuals experiencing speech onset delay, with them performing worse on verbal tasks but adequately or even better than neurotypical individuals on tasks that do not require verbal skills and target nonverbal perceptual reasoning (Box 3) [79]. Conversely, verbal to nonverbal imbalances may also account for a subgroup of individuals with autism who present with sensory-perceptual processing in the normal range and who may show verbal abilities that are comparable or even superior to those in neurotypical individuals [6,88,89]. Beyond verbal to nonverbal imbalances, there remains an active debate on current diagnostic categories of autism, and their implications for research designs and findings (see Box 4.)

A broader approach that integrates different phenotypic features links autism to atypical predictive abilities [90,91]. Accordingly, people with autism have challenges in learning predictive relationships of the external world, which may become overwhelming and affect their ability to

Box 3. Language, intelligence, and autism

About half of people with autism, mostly those diagnosed at preschool age, have a delay in the onset of language, which affects their ability to communicate effectively [107]. However, these children show perceptual interests (e.g., perceptual properties of objects, letters, and numbers) as well as normal and even enhanced visuospatial skills and fluid reasoning. In contrast, one-fifth to one-fourth of autistic people have significantly higher verbal than nonverbal abilities. Delays in the onset of language can further complicate the assessment of their intelligence and lead to underestimation of their cognitive abilities when assessments rely heavily on verbal tasks and instructions. Even people with autism who otherwise have strong verbal skills may struggle to understand and use language in social contexts (such as interpreting sarcasm, carrying on a conversation, or understanding social cues). This can lead to a gap between their verbal intelligence (e.g., the ability to define words or find similarities between concepts) and their ability to use language in everyday interactions, as reflected in higher scores on intellectual than adaptive behaviors. Understanding the interplay between verbal and nonverbal intelligence, language delay, and pragmatics in the context of brain network hierarchies may guide tailored educational and support interventions. For example, a child with strong nonverbal skills but delayed speech may benefit from alternative methods of communication such as picture-exchange systems, speech-generating devices, or the use of written materials to support their communication needs while their verbal skills develop. Similarly, social skills training can help highly verbal individuals with pragmatic challenges to navigate social interactions more effectively, using their cognitive strengths to address their communication difficulties.

interact with it. According to Bayesian models, the influence of prior experiences on perception is reduced in autism. This is possibly due to either a devaluation of prior knowledge or an enhanced weighting of sensory input and leads to perceptions of the world that are atypically grounded in realism [91,92]. The idea that autism-related behaviors involve atypical top-down processing provides an appealing account of cognitive and behavioral alterations in autism and may offer a unified computational framework that is also anchored in brain hierarchies [93,94]. On the other hand, it has been argued that the predictive framework may artificially isolate a particular narrative and then generalize it to a range of perceptual manifestations, some of which are unimpaired. For example, there is evidence that individuals with autism perform comparably to neurotypical individuals when learning statistical regularities in a task that requires predictive learning [95,96]. Furthermore, its account of imbalances in social versus nonsocial dimensions of autism phenotypes remains to be clarified [94].

Evidence from neuroimaging and connectomics research

Using neuroimaging and connectome analyses, there is now an increasing consensus that autism relates to a mosaic of alterations in structural and functional connectivity relative to

Box 4. What are the boundaries of autism?

In the absence of a biomarker that is both sensitive and specific, the boundaries of autism are more a matter of convention than science. Diverse clinical presentations, from severe and recognizable to mild and adapted, are found with the same familial predisposition. The notion of prototypical autism considers the emergent nature of autism [85], which is clinically distinct from more continuous 'autistic traits' [116,124]. It is based on the high degree of clinical similarity between children diagnosed in infancy, who do not speak before the age of 3 or 4 years, and who have relatively specific repetitive behaviors and trajectories. Prototypical autism is also different from adults who do not recognize themselves in this description until late in life, without their family and friends recognizing anything unusual about them until adulthood. At the other extreme of adaptation, a large proportion of neurodevelopmental disorders with identifiable neurogenetic alterations are also positive for the current criteria for autism. These different understandings of the limits of autism have a significant impact on the reported prevalence, which ranges from 1% to 3.5% of the population [1]. Notably, the scientific, clinical, and societal expansion of understanding of autism has been stabilized by the creation of the autism spectrum in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (*DSM-5), which provides a single categorical diagnosis despite variation in intelligence, language, comorbidity, and severity. The DSM-5 was intended to sharpen diagnostic specificity but instead resulted in increased prevalence and heterogeneity [125]. Attempts to classify the autism spectrum into clear subgroups have led to various systems. The DSM-4 divided 'pervasive developmental disorders' into autism, with language delays and limited verbal intelligence; Asperger syndrome, with advanced language but significant social differences; and pervasive developmental disorder not otherwise specified (PDD-NOS), for cases that did not fully fit either category. This approach was abandoned due to disagreements over Asperger syndrome and the broad, inconsistent nature of PDD-NOS. Although a more precise classification could have improved diagnosis and research, the benefits of merging these subgroups in DSM-5 may be less than expected. However, increasing inclusion and size of cohorts has generally taken precedence over the need for homogeneous populations. Coupled with societal pressures to identify more atypical people with autism, the result has been increasingly noisy research populations and a general reduction in the power of scientific evidence about these populations [126].

neurotypicals [12,13]. These changes are generally characterized by underconnectivity of corticocortical systems. In particular, marked connectivity reductions have been described in transmodal systems, such as the default mode network. These findings seem to occur alongside the occurrence of increased connectivity in other circuits, mainly between sensory-motor cortical systems and subcortical regions.

However, there has been high heterogeneity in findings, both across individuals and across different studies [12,97]. This is reflected in a mixed spatial distribution of structural and functional alterations across studies, often not pinpointing a consistent set of areas that are atypically organized in autism. Similarly, there have been variations in the direction of findings, not describing a specific 'signature' either [97,98]. Finally, it remains uncertain whether imaging measures can help explain diverse autism symptoms, because brain–behavior associations so far have not been observed reliably across studies, sites, and measures.

From our perspective, these heterogeneous findings do not imply a limitation of neuroimaging and brain connectivity measures to characterize autism *per se*. They could instead suggest that conventional analysis paradigms, which generally focus on the mapping of alterations in specific areas and/or connections, may be suboptimal to capture conditions such as autism. In fact, individuals with autism may not present with a common 'focal' alteration and hence no strong regional convergence in alterations across groups of individuals mapped to a common spatial template (such as the MNI152 stereotaxic space). This hypothesis would also be supported by studies suggesting increased spatial scattering of functional network organization in autism, a phenomenon previously referred to as increased 'idiosyncrasy' [11,97]. In other words, autism can be understood as a system-level imbalance in network organization across the information-processing hierarchy, where there are alterations in how different levels in the information-processing hierarchy communicate with one another, without necessarily a specific set of regions that are consistently affected across individuals with autism (Figure 2B) [99,100].

To probe hierarchical alterations, recent functional and structural neuroimaging analyses have investigated alterations in cortical gradients in autism (Figure 2C). On the basis of resting-state fMRI connectivity gradient analyses in a multisite dataset, the studies demonstrated a reduced functional differentiation (i.e., a smaller difference in terms of gradient locations) between sensory/motor regions and transmodal systems, such as the default mode network [101], in autism compared with neurotypicals. Individuals with autism studied in that work also presented with connectivity changes potentially indicative of an altered sensory-transmodal signal flow. Specifically, the authors used 'stepwise connectivity' analysis, a technique that sequentially interrogates the evolution of functional connectivity when seeding from sensory systems (such as visual, somatosensory, and auditory systems). In control subjects, progressive steps away from a given sensory seed typically result in a connectivity pattern that becomes increasingly less sensory and eventually converges in the default mode network. In people with autism, on the other hand, stepwise connectivity followed atypical paths and did not selectively converge in the default mode network. The authors could furthermore show that the inability of the default mode network to act as a 'sink' of functional signal flow may relate to weakening of its long-range functional connections, which are otherwise critical for it to function in a cohesive manner.

In the context of prior work questioning the reliability of imaging phenotypes of autism, it is important to emphasize that the aforementioned findings were relatively consistent across the different imaging sites, age ranges studied, and data-processing choices made [101]. Furthermore, the study could identify associations between hierarchical network features and autism-related behavioral characteristics (Figure 2D). Indeed, cortex-wide functional gradients and stepwise connectivity patterns were found to predict total Autism Diagnostic Observation Schedule scores, as well as subscores for social interactions and repetitive and restricted behaviors, even when cross-validation was used [101]. Predictive features were observed in the default mode network, as well as sensory systems, indicating that alterations in both sensory and higher-order regions of the cortical hierarchy may synergistically contribute to autism-related behaviors. As such, cortical hierarchical imbalance may represent an intermediary imaging phenotype that can help explain a broad range of autism atypicalities. Atypical organization of sensory-to-transmodal hierarchies was also suggested in follow-up studies that specifically investigated the connectional organization of specific sensory systems using similar frameworks or when stratifying brain regions with respect to the distance of their functional connections [102,103].

A similar pattern of findings has also been observed in structural network analyses based on diffusion MRI tractography, a technique used to approximate white matter fiber tracts and their spatial organization [104]. Here, alterations were seen in both transmodal systems, such as the default mode network, as well as sensory/motor systems. Interestingly, the changes in cortical structural network patterning were found to co-occur with marked alterations in subcorticocortical connections. Although less frequently studied in previous autism research, the integration of subcortical–cortical interactions into a hierarchical framework will likely be relevant in the understanding of multiple phenotypic facets of autism, notably atypical sensory/perceptual functions as well as repetitive/restrictive behaviors [104]. More broadly, by representing cortical areas along hierarchical gradients, different regional patterns of alterations across individuals, which might otherwise appear difficult to consolidate, may still incur an equivalent hierarchical imbalance when seen as a whole. In other words, hierarchy-based analyses may help to identify a consistent autism phenotype in people presenting with spatially heterogeneous regional alterations (e.g., in the communication of different subregions of the default mode network to sensory systems). This approach may thereby consolidate findings that would appear as mixed and inconsistent and may advance the formulation of coherent brain network endophenotypes in the presence of regional idiosyncrasies.

In a recent study that used task-based fMRI analysis, alterations in the neural representations of hierarchically organized predictions and prediction errors were reported in people with autism relative to neurotypical individuals [105]. In that study, although both individuals with autism and neurotypical individuals made accurate associative learning predictions, the two groups were differently biased by their expectations at the behavioral and neural levels. As such, these functional results paint a complex picture of neural and behavioral alterations at different hierarchical levels, which remain to be confirmed across additional task contexts and analytical paradigms. In future work, it will also be relevant to corroborate these findings with data suggesting prolonged encoding of visual information in autism [3,81] and with data showing a reduced integration of prior beliefs in perceptual inference [92,106].

Concluding remarks

This review summarizes current evidence that autism involves atypical cognitive and neural hierarchies. A hierarchical perspective can help consolidate heterogeneous behavioral presentations of autism, subsume seemingly mixed neuroimaging and connectomics findings, and integrate molecular and system neuroscience approaches. Testing an umbrella account will benefit from increased availability of openly available datasets that ideally combine deep behavioral phenotyping, high-definition neuroimaging, and molecular profiling. This will be facilitated

Outstanding questions

To what extent are hierarchical alterations specific to a given sensory modality? Information-processing hierarchies are thought to be organized by modality prior to cross-modal mixing. This motivates verifying modality-specific versus domain-general imbalances in autism, ideally using 'naturalistic' paradigms.

Do microstructural findings parallel functional changes? Cortical hierarchies are engrained in brain microstructure. Histological and high-field neuroimaging can evaluate such alterations to also determine directional functional flow (e.g., in terms of 'top-down' versus 'bottom-up' signaling).

Do different autism 'subtypes' present with variable hierarchical imbalance? Considering perceptual processing, most marked effects have been reported for autistic individuals with early manifestations, notably those with speech onset delay. Conversely, individuals with a later diagnosis display less pronounced alterations. It may therefore be recommended to test cognitive and imaging hypotheses in cohorts that are stratified by age, clinical certainty, and/or neural substrates themselves.

Are hierarchical imbalances specific to autism? Gradient imbalances have also been reported in other indications. It will thus be relevant to assess the specificity of atypical brain network hierarchy to autism. Such findings might clarify whether certain autism phenotypes are a core aspect of the condition or whether they reflect co-occurring conditions, such as attention-deficit/hyperactivity disorder, which often respond well to stimulant medication.

Do effects vary as a function of birth-assigned sex as well as gender identity? Autism manifests differently in males and females, and brain organizational gradients have also been shown to vary as a function of biological sex, hormonal fluctuations, and sociocultural gender identity. A more nuanced incorporation of sex and gender effects will enhance our understanding of autism's diverse presentations.

by ongoing advances in analytical paradigms and the availability of extensive clinical descriptors and transdiagnostic cohorts to evaluate the sensitivity, specificity, and generalizability of hierarchical imbalances in autism (see Outstanding questions).

Studying alterations in the organization of cognitive and neural information-processing hierarchies may also help to shed light on the distinction between social and nonsocial signs of autism. Early typical cognitive development progressively prioritizes social cues to successfully interact within an interpersonal environment – manifested by ‘communication precursors’ such as joint attention, mutual gaze, orientation to names, and communicative gestures. In contrast, in its most prototypical forms, autism involves a developmental shift toward non–socially biased information processing exemplified by the slow then abrupt disappearance of initiatives toward social interaction. Alternatively, autistic preschoolers present a dominant orientation toward objects, as well as physical and informational aspects of their environment, such as lights, shapes, and movements but also letters and numbers. These perceptually oriented behavior patterns and intense interests in non–socially biased forms of environmental information extend to the common acquisition of nonmaternal language and preference for written language [107]. The long-term consequences of shifting away from typical social biases are most significant for complex social cognition, such as theory of mind. However, as autistic individuals grow older, particularly those who are more verbal, the mastering of and interest in social issues and material are gradually – but variably and unpredictably – regained. Higher-order cognitive control mechanisms required to manipulate complex nonsocial material are relatively spared and sometimes overtly developed, as in savant syndrome.

Although it remains to be established which testable metrics will ultimately characterize autism best and most reliably, ideally these will include measures sensitive to hierarchical processing alterations at the neural level. This could be based on proxies of network hierarchy, including connectome gradient measures [101], together with measures previously described in this context, such as relative activity differences between higher- and lower-order regions or measures of their interconnectivity [108]. For behavioral relevance but also for the context of additional stratification, these measures are ideally complemented by behavioral indices sensitive to discrepancies in verbal versus nonverbal, decoding versus understanding, and social versus nonsocial processing and interest.

Sensory-transmodal hierarchies have also been shown to relate to the expression of different genes and have more generally been shown to relate to susceptibility of pathology and altered genetic programs [22,109,110]. As such, a hierarchical perspective may also help to connect intermediate imaging-based phenotypes to the complex genetic architecture of autism (for a recent review, please see [111]). Such findings may also help to establish the interplay between polygenic mechanisms driven by multiple common variants on the one hand and *de novo* mutations and rare variants on the other hand, as well as their differential contribution to prototypical versus syndromic autism, also in light of comorbid conditions such as epilepsy, attention-deficit/hyperactivity disorder, and anxiety. As such, intermediary phenotypes anchored in large-scale brain organizational properties may circumvent current challenges to translate genetic discoveries into an actionable understanding of autism mechanisms.

One of the advantages of hierarchical models is that they postulate a reorganization of otherwise unaltered functions, which justifies both the absence of a modular deficit of a particular cognitive function and the lack of any specific focal neural substrate. The same idea is expressed by the notion of bias [85], which suggests an inversion or modification of processing priorities and not their deficit. In light of parallel evidence that sensory-social shifts in neurotypical development can be characterized by the emergence and strengthening of sensory-transmodal hierarchies, a hierarchical framework also lends explanatory power to synthesize brain imaging, cognitive, and behavioral findings in autism. This appears to be at least the case in the preschool period (2–5 years old), where autistic signs appear the most prototypically.

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Declaration of interests

The authors have no conflicts of interest to declare.

References

1. Zeidan, J. *et al.* (2022) Global prevalence of autism: a systematic review update. *Autism Res.* 15, 778–790
2. Green, J. (2019) Editorial perspective: delivering autism intervention through development. *J. Child Psychol. Psychiatry* 60, 1353–1356
3. Samson, F. *et al.* (2011) Atypical processing of auditory temporal complexity in autistics. *Neuropsychologia* 49, 546–555
4. Marco, E.J. *et al.* (2011) Sensory processing in autism: a review of neurophysiologic findings. *Pediatr. Res.* 69, 48R–54R
5. Dawson, M. *et al.* (2007) The level and nature of autistic intelligence. *Psychol. Sci.* 18, 657–662
6. Ankenman, K. *et al.* (2014) Nonverbal and verbal cognitive discrepancy profiles in autism spectrum disorders: influence of age and gender. *Am. J. Intellect. Dev. Disabil.* 119, 84–99
7. Joseph, R.M.H. *et al.* (2002) Cognitive profiles and social-communicative functioning in children with autism spectrum disorder. *J. Child Psychol. Psychiatry* 43, 807–821
8. Jaswal, V.K. and Akhtar, N. (2018) Being versus appearing socially uninterested: challenging assumptions about social motivation in autism. *Behav. Brain Sci.* 42, e82
9. Baron-Cohen, S. *et al.* (1985) Does the autistic-child have a theory of mind. *Cognition* 21, 37–46
10. Frith, U. (1997) The neurocognitive basis of autism. *Trends Cogn. Sci.* 1, 73–77
11. Benkarim, O. *et al.* (2021) Connectivity alterations in autism reflect functional idiosyncrasy. *Commun. Biol.* 4, 1078
12. Hong, S.J. *et al.* (2020) Toward neurosubtypes in autism. *Biol. Psychiatry* 88, 111–128
13. Di Martino, A. *et al.* (2014) The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol. Psychiatry* 19, 659–667
14. Muller, R.A. *et al.* (2011) Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders. *Cereb. Cortex* 21, 2233–2243
15. Hilgetag, C.C. and Goulas, A. (2020) 'Hierarchy' in the organization of brain networks. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* 375, 20190319
16. Goulas, A. *et al.* (2018) Cortical gradients and laminar projections in mammals. *Trends Neurosci.* 41, 775–788
17. Bernhardt, B.C. *et al.* (2022) Gradients in brain organization. *Neuroimage* 251, 118987
18. Paquola, C. *et al.* (2019) Microstructural and functional gradients are increasingly dissociated in transmodal cortices. *PLoS Biol.* 17, e3000284
19. Margulies, D.S. *et al.* (2016) Situating the default-mode network along a principal gradient of macroscale cortical organization. *Proc. Natl. Acad. Sci. U. S. A.* 113, 12574–12579
20. Smallwood, J. *et al.* (2021) The default mode network in cognition: a topographical perspective. *Nat. Rev. Neurosci.* 22, 503–513
21. Mesulam, M.M. (1998) From sensation to cognition. *Brain* 121, 1013–1052
22. Sydnor, V.J. *et al.* (2021) Neurodevelopment of the association cortices: patterns, mechanisms, and implications for psychopathology. *Neuron* 109, 2820–2846
23. Park, B.Y. *et al.* (2021) An expanding manifold in transmodal regions characterizes adolescent reconfiguration of structural connectome organization. *Elife* 10, e64694
24. Park, B.Y. *et al.* (2022) Adolescent development of multiscale structural wiring and functional interactions in the human connectome. *Proc. Natl. Acad. Sci. U. S. A.* 119, e2116673119
25. Dong, H.M. *et al.* (2021) Shifting gradients of macroscale cortical organization mark the transition from childhood to adolescence. *Proc. Natl. Acad. Sci. U. S. A.* 118, e2024448118
26. Xia, Y. *et al.* (2022) Development of functional connectome gradients during childhood and adolescence. *Sci. Bull. (Beijing)* 67, 1049–1061
27. Moreau, C.A. *et al.* (2023) Genetic heterogeneity shapes brain connectivity in psychiatry. *Biol. Psychiatry* 93, 45–58
28. Choi, H. *et al.* (2022) Diagnosis-informed connectivity subtyping discovers subgroups of autism with reproducible symptom profiles. *Neuroimage* 256, 119212
29. Muller, R.A. and Fishman, I. (2018) Brain connectivity and neuroimaging of social networks in autism. *Trends Cogn. Sci.* 22, 1103–1116
30. Grill-Spector, K. and Malach, R. (2004) The human visual cortex. *Annu. Rev. Neurosci.* 27, 649–677
31. Felleman, D.J. and Van Essen, D.C. (1991) Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cortex* 1, 1–47
32. Markov, N.T. *et al.* (2013) Cortical high-density counterstream architectures. *Science* 342, 1238406
33. Kveraga, K. *et al.* (2007) Top-down predictions in the cognitive brain. *Brain Cogn.* 65, 145–168
34. O'Callaghan, C. *et al.* (2017) Predictions penetrate perception: converging insights from brain, behaviour and disorder. *Conscious. Cogn.* 47, 63–74
35. Hutchinson, J.B. and Turk-Browne, N.B. (2012) Memory-guided attention: control from multiple memory systems. *Trends Cogn. Sci.* 16, 576–579
36. Mudrik, L. *et al.* (2014) Information integration without awareness. *Trends Cogn. Sci.* 18, 488–496

37. Van Essen, D.C. *et al.* (1992) Information processing in the primate visual system: an integrated systems perspective. *Science* 255, 419–423
38. Rao, R.P. and Ballard, D.H. (1999) Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nat. Neurosci.* 2, 79–87
39. Friston, K. and Kiebel, S. (2009) Predictive coding under the free-energy principle. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* 364, 1211–1221
40. Wacongne, C. *et al.* (2011) Evidence for a hierarchy of predictions and prediction errors in human cortex. *Proc. Natl. Acad. Sci. U. S. A.* 108, 20754–20759
41. Huntenburg, J.M. *et al.* (2018) Large-scale gradients in human cortical organization. *Trends Cogn. Sci.* 22, 21–31
42. Burt, J.B. *et al.* (2018) Hierarchy of transcriptomic specialization across human cortex captured by structural neuroimaging topography. *Nat. Neurosci.* 21, 1251–1259
43. Sheldrick, R.C. and Perrin, E.C. (2013) Evidence-based milestones for surveillance of cognitive, language, and motor development. *Acad. Pediatr.* 13, 577–586
44. Murray, G.K. *et al.* (2007) Infant developmental milestones and subsequent cognitive function. *Ann. Neurol.* 62, 128–136
45. Baum, G.L. *et al.* (2020) Development of structure–function coupling in human brain networks during youth. *Proc. Natl. Acad. Sci. U. S. A.* 117, 771–778
46. Lariviere, S. *et al.* (2019) Multiscale structure-function gradients in the neonatal connectome. *Cereb. Cortex*,
47. van den Heuvel, M.I. *et al.* (2018) Hubs in the human fetal brain network. *Dev. Cogn. Neurosci.* 30, 108–115
48. Oldham, S. *et al.* (2022) Early and late development of hub connectivity in the human brain. *Curr. Opin. Psychol.* 44, 321–329
49. Nguyen, T.T. *et al.* (2024) Variations in cortical functional gradients relate to dimensions of psychopathology in preschool children. *J. Am. Acad. Child Adolesc. Psychiatry* 63, 80–89
50. Vasa, F. *et al.* (2020) Conservative and disruptive modes of adolescent change in human brain functional connectivity. *Proc. Natl. Acad. Sci. U. S. A.* 117, 3248–3253
51. Park, S. *et al.* (2024) A shifting role of thalamocortical connectivity in the emergence of cortical functional organization. *Nat. Neurosci.* 27, 1609–1619
52. Grydeland, H. *et al.* (2019) Waves of maturation and senescence in micro-structural MRI markers of human cortical myelination over the lifespan. *Cereb. Cortex* 29, 1369–1381
53. Sydnor, V.J. *et al.* (2024) A sensorimotor-association axis of thalamocortical connection development. *bioRxiv*,
54. Paquola, C. *et al.* (2019) Shifts in myeloarchitecture characterise adolescent development of cortical gradients. *Elife* 8, e50482
55. Valk, S.L. *et al.* (2017) Structural plasticity of the social brain: differential change after socio-affective and cognitive mental training. *Sci. Adv.* 3, e1700489
56. Valk, S.L. *et al.* (2023) Functional and microstructural plasticity following social and interoceptive mental training. *Elife* 12
57. Kissine, M. (2021) Autism, contructionism, nativism. *Language* 97, 139–160
58. Mueller, S. *et al.* (2013) Individual variability in functional connectivity architecture of the human brain. *Neuron* 77, 586–595
59. Valk, S.L. *et al.* (2022) Genetic and phylogenetic uncoupling of structure and function in human transmodal cortex. *Nat. Commun.* 13, 2341
60. Frazier, T.W. *et al.* (2012) Validation of proposed DSM-5 criteria for autism spectrum disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 51, 28–40 e3
61. American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*, American Psychiatric Association
62. Mottron, L. *et al.* (2006) Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *J. Autism Dev. Disord.* 36, 27–43
63. Shah, A. and Frith, U. (1983) An islet of ability in autistic children: a research note. *J. Child Psychol. Psychiatry* 24, 613–620
64. Robertson, C.E. and Baron-Cohen, S. (2017) Sensory perception in autism. *Nat. Rev. Neurosci.* 18, 671–684
65. Mottron, L. *et al.* (2012) Perception. In *Encyclopedia of Autism* (Volkmar, F., ed.), pp. 2168–2176, Springer
66. Meilleur, A.A. *et al.* (2014) Autism-specific covariation in perceptual performances: 'g' or 'p' factor? *PLoS One* 9, e103781
67. Soulieres, I. *et al.* (2009) Enhanced visual processing contributes to matrix reasoning in autism. *Hum. Brain Mapp.* 30, 4082–4107
68. Cascio, C.J. *et al.* (2012) Perceptual and neural response to affective tactile texture stimulation in adults with autism spectrum disorders. *Autism Res.* 5, 231–244
69. Nakano, T. *et al.* (2012) Superior haptic-to-visual shape matching in autism spectrum disorders. *Neuropsychologia* 50, 696–703
70. Galle, S.A. *et al.* (2013) Olfaction in the autism spectrum. *Perception* 42, 341–355
71. Bernhardt, B.C. *et al.* (2014) Selective disruption of sociocognitive structural brain networks in autism and alexithymia. *Cereb. Cortex* 24, 3258–3267
72. Bird, G. *et al.* (2010) Empathic brain responses in insula are modulated by levels of alexithymia but not autism. *Brain* 133, 1515–1525
73. Silani, G. *et al.* (2008) Levels of emotional awareness and autism: an fMRI study. *Soc. Neurosci.* 3, 97–112
74. Schauder, K.B. *et al.* (2015) Interoceptive ability and body awareness in autism spectrum disorder. *J. Exp. Child Psychol.* 131, 193–200
75. Mottron, L. (2011) Changing perceptions: the power of autism. *Nature* 479, 33–35
76. Mottron, L. *et al.* (2009) Enhanced perception in savant syndrome: patterns, structure and creativity. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* 364, 1385–1391
77. Collignon, O. *et al.* (2013) Reduced multisensory facilitation in persons with autism. *Cortex* 49, 1704–1710
78. Mottron, L. *et al.* (2013) Veridical mapping in the development of exceptional autistic abilities. *Neurosci. Biobehav. Rev.* 37, 209–228
79. Bonnel, A. *et al.* (2010) Enhanced pure-tone pitch discrimination among persons with autism but not Asperger syndrome. *Neuropsychologia* 48, 2465–2475
80. Gui, A. *et al.* (2021) Attentive brain states in infants with and without later autism. *Transl. Psychiatry* 11, 196
81. Marsicano, G. *et al.* (2024) Prolonged neural encoding of visual information in autism. *Autism Res.* 17, 37–54
82. Heaton, P. and Wallace, G.L. (2004) Annotation: the savant syndrome. *J. Child Psychol. Psychiatry* 45, 899–911
83. Baghdadli, A. *et al.* (2003) Relationship between age of recognition of first disturbances and severity in young children with autism. *Eur. Child Adolesc. Psychiatry* 12, 122–127
84. De Giacomo, A. and Fombonne, E. (1998) Parental recognition of developmental abnormalities in autism. *Eur. Child Adolesc. Psychiatry* 7, 131–136
85. Mottron, L. and Gagnon, D. (2023) Prototypical autism: new diagnostic criteria and asymmetrical bifurcation model. *Acta Psychol.* 237, 103938
86. Courchesne, V. *et al.* (2015) Autistic children at risk of being underestimated: school-based pilot study of a strength-informed assessment. *Mol. Autism* 6, 12
87. Girard, D. *et al.* (2023) Visual abilities and exploration behaviors as predictors of intelligence in autistic children from preschool to school age. *Autism* 27, 2446–2464
88. Ostrolenk, A. *et al.* (2017) Hyperlexia: systematic review, neurocognitive modelling, and outcome. *Neurosci. Biobehav. Rev.* 79, 134–149
89. Nader, A.M. *et al.* (2014) Does WISC-IV underestimate the intelligence of autistic children? *J. Autism Dev. Disord.* 46, 1582–1589
90. Van de Cruys, S. *et al.* (2014) Precise minds in uncertain worlds: predictive coding in autism. *Psychol. Rev.* 121, 649–675
91. Palmer, C.J. *et al.* (2017) Bayesian approaches to autism: towards volatility, action, and behavior. *Psychol. Bull.* 143, 521–542
92. Pellicano, E. and Burr, D. (2012) When the world becomes 'too real': a Bayesian explanation of autistic perception. *Trends Cogn. Sci.* 16, 504–510
93. Aitchison, L. and Lengyel, M. (2017) With or without you: predictive coding and Bayesian inference in the brain. *Curr. Opin. Neurobiol.* 46, 219–227
94. Keysers, C. *et al.* (2024) Predictive coding for the actions and emotions of others and its deficits in autism spectrum disorders. *Neurosci. Biobehav. Rev.* 167, 105877

95. Fazioli, L. *et al.* (2025) Suboptimal but intact integration of Bayesian components during perceptual decision-making in autism. *Mol. Autism* 16, 2
96. Pesthy, O. *et al.* (2023) Intact predictive processing in autistic adults: evidence from statistical learning. *Sci. Rep.* 13, 11873
97. Nunes, A.S. *et al.* (2018) Idiosyncratic organization of cortical networks in autism spectrum disorder. *Neuroimage*,
98. Mottron, L. and Bzdok, D. (2020) Autism spectrum heterogeneity: fact or artifact? *Mol. Psychiatry* 25, 3178–3185
99. Lee, J.K. *et al.* (2020) Sex Differences in the amygdala resting-state connectome of children with autism spectrum disorder. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 5, 320–329
100. DiMartino, A. *et al.* Unraveling the miswired connectome: a developmental perspective. 2014. p. 1335-1353.
101. Hong, S.J. *et al.* (2019) Atypical functional connectome hierarchy in autism. *Nat. Commun.* 10, 1022
102. Weber, C. *et al.* (2024) Contracted functional connectivity profiles in autism. *Mol. Autism* 15, 38
103. Park, S. *et al.* (2021) Atypical integration of sensory-to-transmodal functional systems mediates symptom severity in autism. *Front. Psychiatry* 12, 699813
104. Park, B.Y. *et al.* (2021) Differences in subcortico-cortical interactions identified from connectome and microcircuit models in autism. *Nat. Commun.* 12, 2225
105. Sapey-Triomphe, L.A. *et al.* (2023) Neural correlates of hierarchical predictive processes in autistic adults. *Nat. Commun.* 14, 3640
106. Chao, Z.C. *et al.* (2024) Erroneous predictive coding across brain hierarchies in a non-human primate model of autism spectrum disorder. *Commun. Biol.* 7, 851
107. Kissine, M. *et al.* (2023) Language acquisition can be truly atypical in autism: beyond joint attention. *Neurosci. Biobehav. Rev.* 153, 105384
108. Samson, F. *et al.* (2012) Enhanced visual functioning in autism: an ALE meta-analysis. *Hum. Brain Mapp.* 33, 1553–1581
109. Whitaker, K.J. *et al.* (2016) Adolescence is associated with genomically patterned consolidation of the hubs of the human brain connectome. *Proc. Natl. Acad. Sci. U. S. A.* 113, 9105–9110
110. Ball, G. *et al.* (2020) Cortical remodelling in childhood is associated with genes enriched for neurodevelopmental disorders. *Neuroimage* 215, 116803
111. Havdahl, A. *et al.* (2021) Genetic contributions to autism spectrum disorder. *Psychol. Med.* 51, 2260–2273
112. Frith, U. and Happe, F. (1994) Autism: beyond 'theory of mind'. *Cognition* 50, 115–132
113. Frith, U. *et al.* (1991) The cognitive basis of a biological disorder: autism. *Trends Neurosci.* 14, 433–438
114. Mottron, L. and Belleville, S. (1993) A study of perceptual analysis in a high-level autistic subject with exceptional graphic abilities. *Brain Cogn.* 23, 279–309
115. Mottron, L. (2021) A radical change in our autism research strategy is needed: back to prototypes. *Autism Res.* 14, 2213–2220
116. Constantino, J.N. and Charman, T. (2016) Diagnosis of autism spectrum disorder: reconciling the syndrome, its diverse origins, and variation in expression. *Lancet Neurol.* 15, 279–291
117. Vezoli, J. *et al.* (2021) Cortical hierarchy, dual counterstream architecture and the importance of top-down generative networks. *Neuroimage* 225, 117479
118. Goulas, A. *et al.* (2019) The architecture of mammalian cortical connectomes in light of the theory of the dual origin of the cerebral cortex. *Cortex* 118, 244–261
119. Demirtas, M. *et al.* (2019) Hierarchical heterogeneity across human cortex shapes large-scale neural dynamics. *Neuron* 101, 1181–1194.e13
120. Paquola, C. *et al.* (2022) Closing the mechanistic gap: the value of microarchitecture in understanding cognitive networks. *Trends Cogn. Sci.* 26, 873–886
121. Huntenburg, J.M. *et al.* (2017) A systematic relationship between functional connectivity and intracortical myelin in the human cerebral cortex. *Cereb. Cortex* 27, 981–997
122. Cabalo, D.G. *et al.* (2025) Multimodal precision MRI of the individual human brain at ultra-high fields. *Sci. Data* 12, 526
123. Velichkovsky, B.M. (2002) Heterarchy of cognition: the depths and the highs of a framework for memory research. *Memory* 10, 405–419
124. Constantino, J.N. *et al.* (2003) Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. *J. Autism Dev. Disord.* 33, 427–433
125. American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, American Psychiatric Association
126. Rodgaard, E.M. *et al.* (2019) Temporal changes in effect sizes of studies comparing individuals with and without autism: a meta-analysis. *JAMA Psychiatry* 76, 1124–1132