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Sección
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Prefrontal Network Development, Connectome Abnormalities and Heterogeneous Trajectories in Young Adults with Autism: A narrative Review and Testable Conceptual Model

Desarrollo de redes prefrontales, conectopatía y trayectorias heterogéneas en jóvenes adultos con autismo: una revisión narrativa y modelo conceptual contrastable

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Abstract
This narrative review and conceptual contribution examines autism-related developmental trajectories between approximately 15 and 25 years, a period of changing executive demands and continuing development of distributed prefrontal networks. The narrative synthesis distinguishes longitudinal evidence in autistic cohorts from cross-sectional imaging associations, evidence from non-autistic populations, and untested mechanistic proposals. We operationalize connectopathy as potentially atypical age-related coordination of structural, functional, and effective connectivity, including network integration, segregation and dynamic reconfiguration, rather than a universal hypoconnectivity signature. A proposed moderation model predicts that developmental changes in network dynamics will relate to domain-specific daily functioning through executive and emotion-regulation processes, conditional on language, intellectual functioning, support needs, co-occurring conditions and environmental accessibility. Available studies document heterogeneous executive, behavioral and adaptive trajectories, but do not demonstrate this mediation pathway. Prenatal BDNF-zinc-inflammation mechanisms are discussed solely as a non-essential, unconfirmed etiological possibility. We differentiate repetitive autistic behavior from obsessive-compulsive symptoms and treat psychosis as a separate comorbidity rather than an expected developmental consequence. Testable predictions and falsification criteria are specified. Overall, the model is intended to organize prospective research, not to predict individual outcomes from group-level imaging findings.

Keywords: autism; adolescence; prefrontal cortex; executive functions; connectopathy; brain connectivity; emotional regulation; adaptive functioning.

Resumen

Esta revisión narrativa y propuesta conceptual examina las trayectorias del autismo aproximadamente entre los 15 y los 25 años, etapa de demandas ejecutivas cambiantes y desarrollo continuo de redes prefrontales distribuidas. La síntesis distingue los resultados longitudinales en cohortes autistas, las asociaciones transversales de neuroimagen, las extrapolaciones de poblaciones no autistas y las hipótesis mecanicistas aún no verificadas. Se define operativamente la conectopatía como una posible organización atípica, dependiente de la edad, de la conectividad estructural, funcional y efectiva, incluyendo integración, segregación y reconfiguración dinámica de redes, y no como una firma universal de hipoconectividad. El modelo propone que los cambios en la dinámica de redes podrían relacionarse con dimensiones concretas del funcionamiento cotidiano mediante el control ejecutivo y la regulación emocional, con moderación por lenguaje, capacidad intelectual, necesidades de apoyo, condiciones concomitantes y accesibilidad del entorno. Los estudios disponibles muestran trayectorias heterogéneas, pero no demuestran esa cadena mediadora. Los mecanismos prenatales relacionados con BDNF, zinc e inflamación se consideran explicaciones etiológicas complementarias no confirmadas. Se distinguen las conductas repetitivas autistas de las compulsiones y la psicosis se considera una comorbilidad posible, no una consecuencia esperable. Se formulan predicciones contrastables y criterios de refutación sin pretender pronosticar resultados individuales a partir de promedios grupales.

Palabras clave: autismo; adolescencia; corteza prefrontal; funciones ejecutivas; conectopatía; conectividad cerebral; regulación emocional; funcionamiento adaptativo.

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1. INTRODUCTION

Autism is a neurodevelopmental condition whose clinical expression cannot be considered static once childhood is passed, nor can it be interpreted according to a simple dichotomy between presence and absence of the disorder. The diagnosis, in fact, describes a neurodevelopmental configuration that emerges early, but the organization of cognitive, emotional, behavioral, and social functions continues to change during adolescence and early adulthood, in relation to both the biological maturation of the nervous system and experiences, environmental demands, educational and social opportunities, and progressively acquired compensatory strategies. The issue assumes particular relevance between approximately 15 and 25 years of age, a period in which the human brain still undergoes important processes of functional specialization, reorganization of connections, and consolidation of systems responsible for cognitive control, planning, emotional regulation, and evaluation of the consequences of one's actions. It is not, therefore, a matter of affirming that the brain "finishes maturing at twenty-five years," an excessively rigid formulation not supported by developmental neurobiology, but of recognizing that the functional integration of numerous circuits, especially those involving prefrontal regions and their connections with frontoparietal, limbic, striatal, and posterior systems, continues into late adolescence and early adulthood. Trajectories of executive function in the general population indeed show rapid development during the second decade, followed by progressive stabilization around late adolescence and early adulthood, while some processes of specialization and integration continue beyond this phase [1].

This finding becomes particularly interesting when superimposed on the very nature of autism. If the autistic phenotype is at least partly associated with alterations in the organization and integration of brain networks, then adolescent and post-adolescent maturation should not be considered merely as the period in which symptoms "consolidate," but as a phase in which the nervous system can show different modes of compensation, reorganization, and adaptation. The hypothesis of connectopathy in autism, historically developed through models of disconnection between long-distance brain regions and subsequently expanded toward a more complex conception of altered network organization, offers in this sense a useful interpretive framework, provided the term is used as a neurobiological model and not as a synonym for a circumscribed brain lesion. The neuroimaging literature has indeed shown that in autism it is not possible to reduce connectivity to a single linear alteration: anomalies of local and long-distance connectivity, phenomena of hyper- and hypoconnectivity, and important interindividual differences have been described simultaneously, making it more appropriate to speak of altered organization of functional integration rather than simple "disconnection" [2-5].

In this perspective, late adolescence can represent a sort of critical passage in which some difficulties previously compensated by the family and school environment become more evident because the demands for autonomy, self-regulation, and adaptation increase dramatically. During childhood and much of adolescence, many functions can be supported by the external organization provided by adults: relatively predictable schedules, supervision, support in planning, mediation of social relationships, control of daily activities, and protection from the more complex consequences of decisions. With entry into adult life, however, the individual is progressively called upon to autonomously organize behavior,

foresee medium- and long-term consequences, modify plans when conditions change, modulate emotional response, simultaneously manage multiple pieces of information, understand others' intentions, and integrate often conflicting goals. It is precisely at this passage that a difficulty in integrating cognitive, emotional, and motivational systems can acquire greater functional weight than that observable in childhood.

This leads to a conception of the evolution of autism in which the symptom is not necessarily immutable, but neither is it necessarily destined to diminish. Longitudinal research shows, rather, strong heterogeneity. The diagnosis can remain relatively stable, while the severity of some behaviors, communicative ability, adaptive autonomy, compensatory strategies, the impact of psychiatric comorbidities, and the relationship between autistic characteristics and environmental demands change. A systematic review of longitudinal studies in adulthood has found that trajectories are highly variable: cognitive and linguistic abilities can remain relatively stable in some individuals, while adaptive functioning tends to improve in a substantial proportion of subjects, and some studies have observed a reduction in behavioral symptoms of autism over time [6]. Studies on adolescence also indicate that some functions, including components of executive functions and theory of mind, can improve, albeit in the presence of residual difficulties [7]. The fundamental point, therefore, is that development after adolescence does not constitute a simple linear continuation of the infantile phenotype, but a phase in which the relationship between neurobiological vulnerability, brain maturation, and environment can produce different trajectories.

1.1. Scope, Review Approach, and Evidence Appraisal

This article is a critical narrative review integrated with an explicitly hypothesis-generating conceptual model; it is neither a systematic review nor a meta-analysis. The target developmental interval is approximately 15-25 years, selected as a pragmatic transition window rather than a biological maturity threshold. Research extending outside this interval is included only when it informs antecedent mechanisms or subsequent outcomes, and is identified as indirect evidence. The review is not represented as PRISMA-compliant, and it does not claim that the focused literature selection constitutes a reproducible systematic search.

The literature was assembled through focused topic-oriented searches and citation tracking, with additional bibliographic checks conducted in October 2026 using publisher pages, PubMed records and DOI landing pages. Search concepts included autism or autistic, adolescence or emerging adulthood, prefrontal development, executive functioning, structural and functional connectivity, longitudinal outcome, adaptive behavior, emotion regulation and repetitive behavior. Classic conceptual publications were retained alongside peer-reviewed work published mainly during 2020-2026. Selection was purposive: relevance to the proposed developmental relationships, identifiable publication metadata, clarity of sample and design, and capacity to distinguish observation from mechanism were prioritized. No comprehensive database export, predefined protocol, independent dual screening, quantitative risk-of-bias scoring or reproducible flow counts were undertaken; consequently the references cannot be interpreted as an exhaustive corpus and no PRISMA flow diagram is claimed.

Evidence is read at three distinct levels: (i) direct longitudinal observations in autistic people, which can describe developmental change but do not automatically establish mechanisms; (ii) cross-sectional or group-level neuroimaging associations and longitudinal findings from general-population samples, which offer mechanistic plausibility but limited autism-specific inference; and (iii) theoretical etiological proposals, which remain unverified until prospectively tested. Greater interpretive weight is assigned to convergent longitudinal data and transparent syntheses; heterogeneity, confounding, ascertainment bias and measurement limitations are considered when drawing conclusions. The review does not claim that each cited source was retrieved through a single standardized database search.

1.2. Prefrontal Maturation, Executive Control, and Network Integration

The role of the prefrontal cortex in adolescent maturation is particularly relevant because the functions that are progressively required in early adulthood depend on distributed systems and not on a single anatomical region. The prefrontal cortex participates in goal maintenance, planning, inhibition of automatic responses, cognitive flexibility, working memory, behavior monitoring, and evaluation of consequences. These functions, however, emerge from the interaction between prefrontal circuits and other components of the brain, including frontoparietal control networks, striatal circuits, the hippocampus, the amygdala, and networks involved in internal and social processing. The development of executive function must therefore be interpreted as the maturation of an integrated system, in which regional specialization is inseparable from the ability to coordinate information from different circuits. Tervo-Clemmens et al. [1], studying 10,766 participants between 8 and 35 years, identified a general trajectory in which executive function shows particularly rapid development during early and middle adolescence and progressive stabilization around 18-20 years. This does not mean that at twenty the executive system is biologically "finished," but that a substantial part of the quantitative increase in performance is concentrated before this age, while subsequently efficiency, specialization, and integration of circuits become particularly important.

In autism, the issue is more complex. A long tradition of research has identified alterations in executive functions as one of the cognitive characteristics most associated with the condition, although no single executive deficit can be considered specific to autism. Ozonoff et al. [8] were among the first to document executive difficulties in autistic people with relatively high cognitive functioning, opening a line of research subsequently developed by numerous studies. Hill [9] emphasized how the hypothesis of executive dysfunction could not alone explain the entire phenotype, while a very large meta-analysis highlighted significant differences in executive functions in autism, with an overall effect of moderate magnitude [10]. Neuroimaging studies have also linked these difficulties to a different organization of frontoparietal circuits and systems responsible for cognitive control [11, 12]. The most important finding, however, emerges from the longitudinal perspective: a recent systematic review and meta-analysis of 14 longitudinal studies found that autistic children and adolescents generally show lower executive performance compared to controls both at baseline and at follow-up, but did not identify statistically significant between-group differences in longitudinal change for working memory, inhibition, shifting, and planning [13]. Absence of statistical significance does not establish equivalent

developmental trajectories, especially given heterogeneous samples, measures and follow-up intervals; nevertheless, these findings do not support a necessary deterioration of executive abilities with age.

The problem therefore becomes one of integration. A person can over time acquire a better ability to plan a sequence of actions, but still encounter difficulties when they must use that ability in an emotionally intense, socially unpredictable situation, or one characterized by many concurrent pieces of information. Executive function is not only the ability to solve a problem under experimental conditions; in adult life it must be continuously coordinated with emotional regulation, autobiographical memory, future prediction, risk assessment, understanding of social consequences, and the ability to modify a strategy when it does not work. Studies on the development of hippocampal-prefrontal cortex interaction show, for example, that during adolescence some forms of connectivity between the hippocampus and ventromedial prefrontal cortex progressively increase, in relation to processes such as problem solving and future planning [14]. It is precisely this kind of integration that allows past experience to be transformed into a flexible representation of future possibilities. If a network system presents an atypical organization, the difficulty need not necessarily be localized in a single structure, but can reside in the way cognitive, emotional, mnestic, and motivational information is transferred and coordinated between different systems.

Longitudinal neuroanatomical evidence further suggests that adolescence and early adulthood effectively represent a phase of brain reorganization in autism. Wallace et al. [15), longitudinally following autistic adolescents and young adults between 14 and 24 years, observed accelerated cortical thinning in some regions compared to controls, without analogous differences in cortical surface area. These modifications were associated with aspects of daily executive functioning and social symptoms. This result does not demonstrate that cortical thinning is in itself pathological, nor that it constitutes the cause of functional difficulties, but it demonstrates that the trajectory of cortical development in autism can differ during a phase of life in which, even in the general population, the brain is undergoing important reorganization processes. O'Hearn and Lynn [16) further highlighted how brain and cognitive trajectories in autism are heterogeneous and how the cognitive improvements typical of adulthood can be associated with the maturation of frontal, striatal, and temporal systems, with patterns that are not necessarily overlapping in autistic young adults.

In this framework, prefrontal maturation can be understood not as a simple increase in the brain's "power," but as a process of progressive coordination. The adolescent may possess adequate individual cognitive abilities but not yet be able to combine them efficiently under emotional or social load; the young adult may instead develop a greater ability to use these resources in an integrated manner. This distinction is fundamental for understanding why some autistic people show progressive acquisition of autonomy during the second decade, while others manifest more marked difficulties precisely when the environment stops providing a sufficiently containing external structure. The change observed in adulthood can therefore be interpreted not only as "improvement" or "worsening" of the symptom, but as a change in the relationship between internal capacities and environmental demands.

1.3. Connectopathy, Plasticity, and Divergent Trajectories

The notion of connectopathy allows shifting attention from the question "which area of the brain functions poorly?" to the question "how is information integrated between different systems?" The term must be used with caution, because autism does not present a single connectivity signature valid for all individuals. The neuroimaging literature has shown heterogeneous and sometimes apparently contradictory results, with evidence of both hypoconnectivity and hyperconnectivity and with differences that depend on age, experimental paradigm, network studied, and individual characteristics. The fronto-posterior underconnectivity model proposed by Just et al. [4] played an important historical role in the interpretation of autism as a disorder of the organization of distributed neural systems, while Hull et al. [5] subsequently emphasized the complexity of resting-state functional connectivity findings. The most prudent conclusion is therefore that autism may include, in a proportion of individuals, alterations in functional integration between networks, without this implying a single or universal configuration.

The perspective proposed by Di Salvo [17] develops a specific hypothesis according to which a dysregulation of BDNF, inserted in a cascade comprising genetic susceptibility, prenatal neuroinflammation, and alterations in zinc homeostasis, could contribute to the atypical organization of synaptic connectivity. The methodologically important point of the proposal is that it is explicitly presented as an integrative hypothesis and not as a demonstrated theory. In the author's material, findings supported by relatively robust evidence are indeed distinguished from observational associations and speculative inferences, recognizing that evidence relating to BDNF, neuroinflammation, and zinc is heterogeneous and that the model cannot be considered universal. This caution is essential even when the hypothesis is transferred from the prenatal period to the understanding of subsequent trajectories: a connectopathy hypothesized as a consequence of early processes is not equivalent to maintaining that the adult brain remains immutable or that a specific molecular alteration necessarily determines a specific behavior.

The concept becomes particularly useful instead if considered in relation to plasticity. An initial alteration in the organization of connections can produce a different distribution of cognitive and behavioral strategies, but the nervous system remains capable of reorganization. Experience, learning, exposure to different contexts, and the development of compensatory strategies can modify the way networks are used. Consequently, the presence of a connective vulnerability does not necessarily imply a negative functional outcome. On the contrary, two individuals with partially overlapping neurobiological characteristics can develop very different trajectories depending on the cognitive, linguistic, environmental, and relational resources available. This is consistent with the literature on adult outcomes, which shows notable heterogeneity and high variability between studies [6, 18].

A favorable trajectory can therefore be conceived as the result of a progressive increase in the efficiency with which cognitive resources are integrated with emotional and contextual information. The person may continue to present autistic characteristics, but develop a better ability to anticipate difficulties, build flexible routines, use compensatory strategies, recognize emotional states, plan and correct behavior. In this sense, prefrontal maturation may not eliminate the underlying vulnerability, but increase the capacity to govern it. An

unfavorable trajectory, on the contrary, could emerge when the increase in environmental demands exceeds the system's capacity to effectively integrate information, especially in the presence of comorbidities, anxiety, sleep disorders, social isolation, chronic stress, or insufficient environmental support. It would therefore not be correct to describe the second pathway as a "degeneration" of autism: it would be more appropriate to speak of a condition in which neurodevelopmental vulnerabilities become more functionally relevant because the context requires higher levels of autonomy and self-regulation.

This model also allows understanding why some behaviors may seem to intensify in early adulthood without this necessarily implying an increase in the underlying autistic characteristic. Repetitive behaviors and the search for predictability can serve different functions at different moments of development. Under conditions of high uncertainty, repetition can contribute to the stabilization of behavior and the reduction of cognitive or emotional load. If, however, cognitive flexibility and emotional regulation do not increase in parallel with environmental complexity, a strategy that was initially adaptive can become excessively rigid and limiting. The relationship between repetitive behavior and emotional regulation is therefore bidirectional: repetition can reduce uncertainty, but a low capacity to tolerate uncertainty can in turn increase dependence on repetition.

1.4. Operational Definitions, Mechanistic Boundaries, and Model Predictions

For this article, connectopathy denotes a candidate deviation in the organization or developmental change of distributed brain networks, measured across three non-interchangeable domains. Structural connectivity refers to properties of anatomical pathways assessed, for example, by diffusion MRI tractography, which estimates white-matter architecture but not synaptic transmission. Functional connectivity refers to statistical covariation of regional signals, such as resting-state fMRI correlations, which does not itself establish a causal influence. Effective connectivity refers to model-dependent estimates of directed influence between regions during specified states or tasks; its inference depends strongly on the adopted model and data quality. Atypicality in one domain does not imply atypicality in the others. A 2024 multimodal study in autistic children reported associations between dynamic neural-network features and subsequent adaptive measures [30]; it is relevant to measurement feasibility but cannot validate the present 15-25-year trajectory model, as its population and methods differ.

Network integration may be operationalized through whole-brain efficiency, participation coefficients or cross-network communication indices; segregation through modularity and within-network coherence; and dynamic reconfiguration through reproducible changes in network coupling across task demands or time. These indices are sensitive to motion, preprocessing, parcellation, physiological noise and sampling choices, and may not have interchangeable interpretations. An atypical population mean is not a diagnostic biomarker and cannot establish the presence, direction or clinical significance of a network difference in an individual. Compensation is defined here as improvement in task performance or ecological functioning despite persistent measured vulnerability, potentially supported by alternative strategies, network recruitment or environmental accommodation; evidence of functional improvement alone cannot identify its neural mechanism.

The specific contribution of the proposed model is a moderated longitudinal mediation hypothesis, not the generic claim that maturation and environment interact. Conditional prediction 1: within-person improvement in age-sensitive measures of network reconfiguration from 15 to 25 years will precede, and statistically predict, improvement in ecologically assessed flexibility or emotion regulation, after controlling for baseline scores and confounding variables. Prediction 2: executive flexibility and emotion regulation will partly mediate associations between network change and domain-specific adaptive outcomes; the pathway may be absent or different in specific profiles. Prediction 3: environmental predictability, accessible support and co-occurring anxiety or sleep difficulties will modify the strength or direction of observed associations. These predictions are not findings of the present review. Existing dynamic-connectivity findings in autistic childhood [30] and developmental neuroimaging in mixed or non-autistic adolescent samples [33] motivate specific measurements, but neither directly confirms longitudinal mediation between ages 15 and 25 in autism.

The model would be weakened by preregistered, adequately powered multisite longitudinal results showing no replicable association between within-person network dynamics and later domain-specific adaptation, stable null mediation across valid measures, or explanatory performance no better than models based on baseline functioning and environment alone. Observations of both hyper- and hypoconnectivity, by themselves, neither confirm nor refute the model. Causal claims would require stronger experimental or quasi-experimental identification strategies; predictive success alone does not prove neural mediation.

1.5. Emotional Regulation, Rigidity, and Obsessive-Compulsive Phenomena

Emotional regulation constitutes probably one of the domains in which the integration between prefrontal cortex and subcortical systems becomes most evident. Regulating an emotion does not simply mean suppressing it, but recognizing the internal state, attributing meaning to it, modulating the intensity of the response, selecting a strategy, and modifying it if ineffective. The prefrontal cortex participates in this process through interactions with the amygdala, striatum, insula, and other components of networks involved in salience evaluation and behavior regulation. In autism, significant difficulties in emotion regulation have been described, associated with maladaptive behaviors and increased functional load [19, 20]. Emotional regulation, moreover, is not separable from executive functions: when the level of emotional activation increases, it becomes more difficult to maintain working memory, inhibit an immediate response, consider alternatives, and modify an already initiated strategy. This leads to a possible circle in which an executive vulnerability increases emotional dysregulation and emotional dysregulation, in turn, further reduces the efficiency of executive control.

In this perspective, it is possible to better understand the persistence of rigidity. Autistic rigidity should not automatically be interpreted as an obsessive-compulsive phenomenon. The restricted and repetitive behaviors of autism and the obsessions and compulsions of obsessive-compulsive disorder may have similar surface phenomenological characteristics, but differ in motivation, subjective experience, function, and relationship with anxiety. Jiujias et al. [21) emphasized precisely the need to distinguish these phenomena. In autism,

repetition can be associated with the search for predictability, sensory regulation, pleasure, circumscribed interest, or reduction of uncertainty; in obsessive-compulsive disorder, on the other hand, compulsions are generally linked to intrusive obsessions or a need to neutralize a perceived threat. The distinction is clinically important because it prevents interpreting every ritualized behavior as an obsessive-compulsive disorder and, at the same time, allows recognizing when a true obsessive-compulsive comorbidity appears in an autistic person.

It is nevertheless plausible to hypothesize that a reduced integration between control systems, emotional systems, and circuits involved in salience evaluation may increase vulnerability to increasingly rigid forms of repetitive behavior, especially when environmental demands increase. This remains an interpretive model and not a causal demonstration. The multimodal meta-analysis by Carlisi et al. [22], which compared structural and functional anomalies in autism and obsessive-compulsive disorder, indeed shows both areas of overlap and differences between the two conditions. The possible relationship between connectopathy, rigidity, and obsessive-compulsive phenomena should therefore be studied through longitudinal measures that accurately distinguish the different clinical phenomena rather than using a single category of "repetitiveness."

The same reasoning can be applied to more severe emotional dysregulation. Di Salvo [23] examined emotional dysregulation in neurodevelopmental disorders as a transdiagnostic phenomenon, emphasizing its relationship with daily functioning, long-term outcomes, and quality of life, as well as the need to consider different mechanisms underlying the same behavioral manifestation. In this perspective, the clinically most useful question is not simply how "dysregulated" a person is, but which process is fueling that dysregulation: sensory overload, difficulty in emotional recognition, cognitive inflexibility, anxiety, problem-solving deficits, communicative difficulties, sleep alterations, or environmental demands exceeding available resources. The advantage of a network perspective consists precisely in the possibility of avoiding monocausal explanations.

A further development concerns the possibility that poor functional integration of control systems makes it more difficult to distinguish between internal experience, emotional interpretation, and information coming from the environment. Even in this case, however, it is not scientifically correct to maintain that failed prefrontal integration necessarily "produces" psychosis. The association between autism and psychotic phenomena is documented, but it is extremely heterogeneous and presents important diagnostic and phenomenological problems. Communicative difficulties, alexithymia, atypical sensory experiences, idiosyncratic thinking, and some modes of social interpretation can complicate the distinction between autistic characteristics and psychotic symptoms. Ribolsi et al. [24] emphasized precisely the need for accurate clinical recognition of psychosis in autism, while the recent meta-analysis by Miles et al. [25], comprising 63 studies and millions of participants aggregated across different samples, highlighted an association between autism and psychosis but also marked heterogeneity and relevant problems relating to measurement instruments. It is therefore more correct to formulate the hypothesis according to which some configurations of neurocognitive vulnerability, associated with emotional dysregulation, difficulties in information integration, and psychiatric comorbidities, may increase vulnerability to psychotic experiences in a subpopulation of autistic people, without transforming this possibility into a general causal relationship.

1.6. Etiological Hypotheses and the Limits of Developmental Inference

The proposed prenatal cascade involving genetic susceptibility, maternal immune activation, zinc homeostasis and BDNF signaling [17, 29] is one optional etiological narrative, not an indispensable premise of the 15-25-year developmental model. Its constituent mechanisms have different levels of evidential support and their joint causal sequence has not been established in a prospective human cohort. Neither peripheral biomarker associations nor animal-model mechanisms establish that a particular prenatal pathway determines later human network integration. The model is therefore compatible with multiple etiological routes producing partly overlapping developmental phenotypes.

A decisive missing evidential bridge is a longitudinal design linking prospectively measured prenatal exposures or molecular markers to repeated adolescent network measures and, independently, to subsequent adaptive outcomes. Such a design would need to examine confounding by genetic background, family circumstances, co-occurring conditions and medication, with preregistered mediation tests and replication. Until such evidence exists, the prenatal pathway cannot explain observed differences between autistic individuals aged 15-25 and must not be conflated with the direct longitudinal findings discussed here.

1.7. From Late Adolescence to Adulthood: Why Some Pathways Diverge

The transition between adolescence and early adulthood thus represents a period in which the functional meaning of autistic characteristics can change. A difficulty that during secondary school is compensated by the presence of an external structure can assume greater weight at university, at work, or in the autonomous management of daily life. The individual must simultaneously plan, organize, tolerate the unexpected, manage less structured social relationships, face economic and professional decisions, and build an adult identity. Executive functions thus become a sort of interface between neurobiological vulnerability and the environment. It is not enough to possess good memory or good abstract reasoning: one must be able to coordinate multiple cognitive and motivational systems in real time.

Available outcomes clearly show that this transition is highly heterogeneous. The meta-analysis by Mason et al. [18], comprising 18 studies and 1,199 autistic people, estimated separate pooled meta-analytic estimates of 20.0% good, 26.6% intermediate, and 49.3% poor outcomes; these weighted category-specific estimates should not be interpreted as one mutually exclusive distribution from a single sample and need not sum to 100%. These percentages must, however, be interpreted with caution, because heterogeneity between studies was very high and the outcome categories used do not necessarily coincide with contemporary concepts of quality of life, self-determination, or adaptation. It is therefore improper to translate the data into an individual prediction and equally improper to conclude that about half of autistic people “worsen” after adolescence. The data rather document the presence of a significant proportion of adults who, in the longitudinal samples studied, achieve limited levels of autonomy and global functioning. A previous review had already found great variability in adult outcomes and a tendency toward improvement in adaptive functioning in many studies [6].

A particularly interesting picture emerges from the prospective study by Forbes et al. [26], which followed 121 autistic people from age 12 to age 23. At 23, 36% were in competitive employment or education, 54% had frequent contact with friends, only 5% lived independently, and 37% needed assistance during the night. The overall outcome was "good" or "very good" in 49% of the sample, "fair" in 37%, and "poor" in 15%. This study is particularly useful because it shows how reductive it is to use a single variable to describe the adult condition: a person can have good occupational functioning but low residential autonomy; can have good cognitive levels but persistent social difficulties; can improve in behavior without achieving independence; or can maintain evident autistic characteristics and at the same time achieve a satisfactory quality of life.

The discrepancy between different domains of functioning is precisely what a network perspective allows interpreting. Adult autonomy depends not only on intellectual level nor only on the severity of autistic symptoms. It depends on the interaction between executive functions, language, adaptive capacities, emotional regulation, mental health, social support, and environmental demands. Forbes et al. [26] also found that infantile characteristics, intellectual quotient, and adaptive functioning allowed relatively useful predictions for some outcomes, such as residential and occupational situation, while prediction was much weaker for friendships, mental health, and some aspects of quality of life. This result suggests that adult trajectories are not completely determined by characteristics observable in childhood.

Problem behaviors can also change over the course of development. A longitudinal meta-analysis by Adams et al. [27], comprising 56 studies, found a small but significant reduction over time in challenging behaviors in autistic children and adults, with greater decreases in studies characterized by longer follow-ups and more advanced age at follow-up. This result also does not authorize speaking of a "cure" from autism, but indicates that some behavioral manifestations can attenuate over the course of development. The distinction between core features, associated behaviors, and functional adaptation is therefore fundamental: a reduction in a repetitive or aggressive behavior does not necessarily imply a modification of the underlying neurodivergence, just as the persistence of the diagnosis does not imply the unchanged persistence of every behavioral manifestation.

The model of divergent trajectories can therefore be formulated in dynamic terms. A first possibility is that in which the maturation of control systems and experience allow greater integration between brain networks and better use of compensatory strategies. In this scenario, autistic characteristics may remain present, but the person develops a growing ability to manage them. A second possibility is that in which cognitive maturation proceeds but a significant difficulty remains in the integration between executive control, emotional regulation, and flexibility, with consequent dependence on routines, repetitive strategies, and external supports. A third possibility is that in which, in the presence of more marked vulnerabilities and psychiatric or environmental comorbidities, the growing complexity of adult life determines a relative loss of adaptation: not necessarily because the brain "worsens," but because the relationship between available capacities and environmental demands becomes less favorable.

This last point is particularly important because it avoids a frequent confusion between neurological development and social functioning. A person can show improvement in cognitive functions and simultaneously experience greater difficulty in daily life, simply because demands increase more rapidly than available capacities. Similarly, a person can present persistent difficulty in social cognition but achieve high autonomy through compensatory strategies, environmental supports, and structuring of daily life. The concept of outcome must therefore be multidimensional and cannot be reduced to a single index of "severity."

1.8. Population Heterogeneity and Outcome Constructs

The proposed relationships cannot be generalized uniformly across the autism spectrum. Cohorts differ in baseline intellectual functioning, expressive and receptive language, communication modalities, support needs, sex and gender composition, psychiatric co-occurrence, medication exposure and access to services. Task-based neuroimaging and formal executive testing can systematically exclude individuals with intellectual disability, limited spoken language, marked sensory intolerance or higher daily support needs. Analyses should therefore report subgroup composition, recruitment mechanisms and missingness, and test moderation rather than assume that group-average effects apply across profiles.

Adaptive functioning concerns practical, conceptual and social skills expressed in daily contexts; autonomy concerns agency and opportunities to act with appropriate supports; independence refers to the level of assistance needed for particular tasks; subjective well-being and quality of life include personally meaningful outcomes; self-determination concerns choice and control over decisions. These are distinct constructs. High residential or personal support needs need not imply poor quality of life, lack of autonomy or developmental failure. Proposed longitudinal outcome batteries should combine standardized adaptive scales, person-reported quality-of-life and agency measures, accessible communication methods, and contextual measures of barriers and supports. Employment or residence alone should not serve as a proxy for global outcome. A systematic review of quality-of-life measurement found frequent proxy reporting, limited accessibility adaptations and underrepresentation of participants with intellectual and communication disabilities [31]. A recent validation study of choice-making opportunities among autistic adults offers a distinct operational indicator of agency, rather than a substitute for quality of life or adaptive skills [32].

1.9. An Integrative Model for Early Adulthood

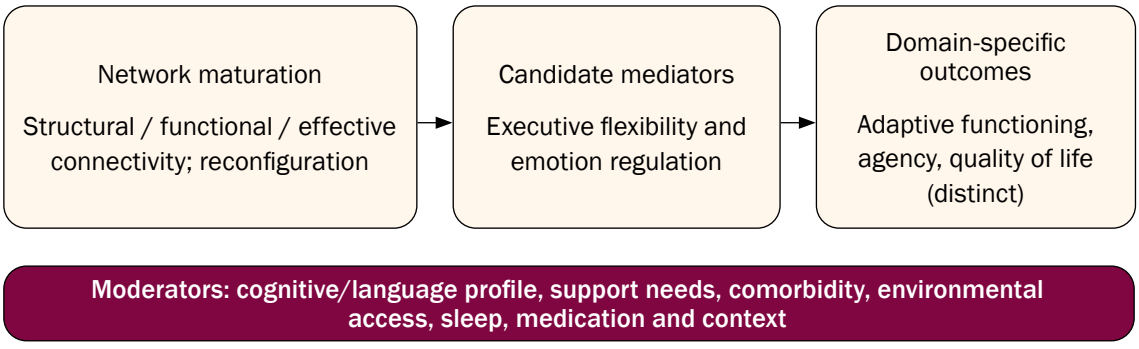
The set of these observations allows proposing a model in which late adolescence and early adulthood represent a particularly significant developmental window for understanding the relationship between neurobiology and behavior in autism (see Figure 1). At the base, a neurodevelopmental vulnerability can be hypothesized, characterized, at least in a proportion of individuals, by a different organization of connectivity and network integration. The hypothesis of Di Salvo [17] places a possible origin of this connectopathy in an interaction between genetic predisposition, prenatal neuroinflammation, zinc homeostasis, and BDNF dysregulation; this proposal must, however, remain distinct from consolidated data on

connectivity in autism, because the complete causal chain has not been demonstrated and the model itself recognizes the presence of discordant results and possible biologically different subgroups. Downstream of this early vulnerability, adolescent maturation can progressively modify the efficiency of control systems, the ability to integrate information, and the possibility of compensating for difficulties through cognitive and environmental strategies.

In this framework, the prefrontal cortex should not be considered a "center" that unilaterally controls behavior, but a component of distributed systems that allow integrating goals, emotions, memory, motivation, and social information. The maturation of prefrontal circuits can therefore increase the ability to coordinate the different components of behavior without necessarily modifying the original neurobiological vulnerability. It is this distinction that allows understanding why a person can progressively improve in planning and simultaneously maintain marked sensory sensitivity, a strong preference for predictability, or difficulty in social cognition. Development does not necessarily erase the neurodevelopmental configuration, but can profoundly modify its functional expression.

Connectopathy, in this sense, can be conceived as a vulnerability to integration rather than as a simple loss of connections. If brain networks succeed in coordinating more effectively during development, the individual can acquire greater flexibility and control; if such integration remains inefficient, the person may depend more on repetitive strategies and predictable environmental structures. Under conditions of strong stress, the difficulty of integration could make more likely the passage from an adaptive strategy to a rigid or disorganized response. This does not imply a deterministic relationship: the same vulnerability can be compensated differently depending on individual resources and the environment.

Figure 1. Conceptual longitudinal model (testable hypothesis, not an established pathway)



Source: own elaboration

The most interesting hypothesis to be subjected to empirical verification therefore concerns not the simple presence of greater or lesser connectivity, but the ability of a network to flexibly pass from one functional state to another. Adult life indeed requires not only connection, but also selective disconnection, specialization, and reconfiguration. An efficient brain must be capable of integrating information when necessary and segregating systems when functional separation is advantageous. A connectopathy could therefore concern not only a reduction in long-distance connectivity, but an altered dynamic relationship

between integration and segregation of networks. This formulation is more coherent with the heterogeneity observed in neuroimaging studies and allows overcoming the simplistic dichotomy between “hyperconnectivity” and “hypoconnectivity.”

From this point of view, the trajectory between approximately 15 and 25 years should be studied through a combination of longitudinal neuroimaging, neuropsychological measures, and ecological assessments of daily functioning. It would be particularly useful to simultaneously follow structural and functional connectivity, executive functions, emotional regulation, cognitive flexibility, repetitive behaviors, obsessive-compulsive symptoms, anxiety, sleep quality, possible psychotic symptoms, and indicators of adaptive autonomy. A design of this type would allow verifying whether determined patterns of prefrontal network maturation are associated with different functional trajectories and, above all, whether the ability to integrate networks predicts the transition toward greater autonomy independently of the persistence of the diagnosis.

A further important element is the need not to excessively separate neurobiology and environment. If brain maturation increases the capacity for regulation and flexibility, the environment must simultaneously allow these capacities to be used. An excessively unpredictable, socially hostile, or unsupportive context can increase functional load and make vulnerabilities more evident. Conversely, an environment sufficiently predictable but not rigidly limiting can allow the person to use emerging capacities without requiring continuous compensatory investment. The perspective developed by Di Salvo [23] on emotional dysregulation is coherent with this approach, since it considers dysregulation as a multifactorial phenomenon requiring individualized assessment of biological, cognitive, and environmental components.

It is also important to avoid a purely deficitological conception of development. The fact that a person maintains autistic characteristics in adulthood does not mean that development has failed. Neurodiversity does not coincide with the absence of difficulties and does not require denying the suffering associated with the most severe forms of autism, but it requires distinguishing neurodivergence from functional disability produced by the interaction between individual characteristics and environment. In this direction, the model proposed by Di Salvo [28] on repetitive conducts as possible adaptive feedback processes can be used as a further interpretive element: some behaviors can consolidate because they reduce uncertainty or emotional load, becoming however progressively less flexible when used as an almost exclusive regulation strategy. The problem would therefore not be repetition itself, but the reduction of the available adaptive repertoire.

Even the possibility of obsessive-compulsive or psychotic phenomena must be inserted into the same model without transforming it into an inevitable consequence of connectopathy. A difficulty in information integration can be theoretically relevant for emotional regulation, cognitive flexibility, and salience evaluation, but the passage from these vulnerabilities to a specific clinical syndrome depends on numerous other factors. Psychosis, in particular, requires a distinct phenomenological evaluation and cannot be deduced from the simple presence of rigid thinking, restricted interests, atypical sensory experiences, or social difficulties. The most recent literature indeed suggests an association between autism and psychosis, but also notable heterogeneity and measurement problems that require great interpretive caution [24, 25].

1.10. Limitations of the Review and Proposed Model

This non-systematic narrative synthesis is vulnerable to selective inclusion, publication bias and interpretive weighting; it cannot estimate pooled effects or establish completeness of coverage. Neuroimaging findings come substantially from cross-sectional samples, variable acquisition and analysis pipelines, and cohorts that often underrepresent people with greater support needs. Even longitudinal associations cannot by themselves determine whether network change causes change in behavior, reflects common developmental processes or follows learning and environmental adaptation. Prospective developmental neuroimaging in a non-autistic adolescent sample links continuing cortical and network change with psychosocial functioning [33], but such findings should not be transposed directly to autistic adults.

The conceptual model combines measures obtained from different samples, ages and analytic traditions, and its proposed mediation chain has not been evaluated as an integrated prospective test. Effects of medication, psychiatric co-occurrence, sleep, family resources, language, gender-related ascertainment and support availability may confound or moderate apparent trajectories. Construct validity is also a challenge: structural connectivity, functional coupling, adaptive functioning, independence and subjective quality of life should not be treated as interchangeable variables. These limitations restrict both individual-level clinical inference and generalization across autistic populations (see Table 1).

Table 1. Selected longitudinal evidence and limits of inference

Study (citation)	Design/population	Finding relevant to trajectory	Limit of inference
Wallace et al. (15)	Longitudinal structural MRI; autistic adolescence/ early adulthood	Different cortical thinning trajectories in selected regions	Imaging correlate; not causal mechanism or individual predictor
Yeung et al. (13)	Systematic review/meta-analysis of longitudinal executive measures	Between-group deficits; no statistically significant group difference in selected slopes	Nonsignificant difference is not proof of equivalence
Forbes et al. (26)	Prospective cohort from childhood to age 23	Markedly different employment, relationship and residence outcomes	Single cohort; domains and supports are not interchangeable
Mason et al. (18)	Meta-analysis of adult-outcome studies	Category-specific pooled estimates vary substantially	Heterogeneous operational outcome categories
Adams et al. (27)	Systematic review/meta-analysis of longitudinal behavioral studies	Small average reductions in challenging behavior	Does not identify underlying neural change
Wan et al. (30)	Longitudinal outcome association; dynamic EEG/ fNIRS in autistic children	Dynamic network features associated with adaptive development	Indirect to ages 15-25; non-causal and distinct measurement modalities

Source: own elaboration

2. CONCLUSIONS

Late adolescence and early adulthood constitute a crucial phase for understanding the evolution of autism because they coincide with an advanced phase of maturation of brain systems responsible for executive control, emotional regulation, planning, and integration of information from different networks. The prefrontal cortex continues to be involved in this process, but it would be reductive to speak of a simple "frontal maturation": what progressively becomes more important is the integration of prefrontal circuits with frontoparietal, limbic, striatal, hippocampal, and posterior networks. Available evidence indicates that executive functions can improve during development even in autism, while remaining on average more vulnerable compared to controls, and that adolescent brain trajectories can present characteristics different from those observed in typical development [1, 13, 15].

Connectopathy constitutes in this framework a possible integrative model, but it must be understood as an alteration of the organization and integration of networks rather than as a simple disconnection. The proposal of a relationship between prenatal neuroinflammation, BDNF dysregulation, zinc homeostasis, and the organization of connections represents an interesting theoretical hypothesis, but it must remain distinct from the level of available evidence. The same formulation of Di Salvo [17] recognizes that the proposed cascade cannot be considered universal and that causal relationships remain to be demonstrated. This distinction is essential because it allows using the model as a hypothesis generator without prematurely transforming it into a definitive etiological explanation of autism.

The central point of the developmental perspective is therefore that maturation after adolescence can produce different trajectories. In some individuals, the progressive integration of control systems can translate into greater flexibility, better emotional regulation, and greater autonomy; in others, a persistent difficulty in integrating executive control, emotional systems, and contextual information can maintain a strong dependence on predictability, routines, and repetitive behaviors. In the presence of high stress or comorbidity, such vulnerabilities can become more evident. It is possible to hypothesize that, in specific subgroups, an inefficient functional integration contributes to the persistence or aggravation of rigidity, emotional dysregulation, and obsessive-compulsive phenomena, while the possible appearance of psychotic phenomena must be considered a possible comorbidity or an associated trajectory, not a necessary consequence of connectopathy.

Data on adult outcomes confirm above all the heterogeneity of the phenomenon. Aggregate estimates from longitudinal studies show a significant proportion of people with limited autonomy, but also a consistent presence of trajectories characterized by functional, occupational, or adaptive improvements. Variability between domains is often greater than variability summarized in a single outcome category. A person can therefore improve in cognitive functions and continue to need residential support; can maintain important autistic characteristics and achieve good employment; can have good linguistic abilities but severe emotional vulnerability; or can present significant adaptive disability despite a relatively high intellectual level. The notion of "outcome" must therefore be replaced, when possible, by a multidimensional description of the individual trajectory.

The most productive perspective for future research therefore consists in following individuals longitudinally from late adolescence until at least the middle of the third decade of life, integrating measures of brain connectivity, executive functions, emotional regulation, repetitive behaviors, psychiatric comorbidities, and adaptive functioning. The goal should not simply be to establish whether the autistic brain "matures" or not, but to verify how different configurations of maturation and network integration are associated with different forms of adaptation. The fundamental question thus becomes whether the process of prefrontal and fronto-subcortical development succeeds in compensating, at least partially, for a pre-existing connective vulnerability or whether, in certain subgroups, integration remains sufficiently inefficient to make it more difficult to manage the growing demands of adulthood.

In definitive terms, autism after adolescence should not be represented either as an immutable condition or as a disorder naturally destined to diminish. It is more plausible to consider it as a neurodevelopmental trajectory in which brain maturation, plasticity, learning, compensation, and environment continuously interact. The period between late adolescence and twenty-five years can represent a particularly important window because, while some components of executive function reach relative stabilization, the integration of networks and the ability to use these systems in real, complex, and unpredictable situations continue to consolidate. It is precisely in this space between neurobiological maturation and environmental demand that adult trajectories of autism can diverge. Understanding this divergence therefore requires overcoming both an exclusively behavioral vision and an exclusively localizationist vision of the brain, adopting a model in which connectivity, prefrontal development, emotional regulation, cognitive flexibility, and adaptation are considered interdependent components of the same developmental process.

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