Running title:

A Framework for Neurodevelopmental Disorders: Operationalization of a Pathogenetic Triad

Short title:

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ADHD = Attention-Deficit/Hyperactivity Disorder

BAP = Broader Autism Phenotype

CC = Cognitive Capacity

HCF = Higher Cognitive Functions

HRV = Heart Rate Variability

NB = Neuropathological Burden

NDD = Neurodevelopmental Disorder

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A Framework for Neurodevelopmental Disorders: Operationalization of a Pathogenetic Triad

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ABSTRACT

Neurodevelopmental disorders are characterized by abnormal neural development leading to lifelong behavioral and cognitive issues. Both endogenous and exogenous factors have been shown to influence their development, and their effects have been extensively discussed. Despite this, an explanatory model does not exist. The lack of a clinically relevant framework underscores difficulties in explaining research findings as well as conundrums including heterogeneity, sex ratio differences, optimal outcome prediction, and findings such as loss of diagnosis, and onset beyond early childhood.

This paper presents a model for conceptualizing the pathogenesis of neurodevelopmental disorders from the interaction of a triad of contributing factors: genetic susceptibility, cognitive compensation, and risk factors. The factors are operationalized to create a clinically relevant framework and approaches for quantification of each operationalized factor are presented. This allows clinicians to implement the framework in a practical setting, potentially improving diagnostics, and provides researchers with an explanatory framework for the conundrums mentioned above. An approach to stratification is proposed through the operationalization of risk factors. Finally, methods for testing and validation of the triad are outlined.

1. Introduction

Neurodevelopmental Disorders (NDD) are characterized by strong biological underpinnings, such as high heritability and various neurobiological alterations, that give rise to maladaptive behavioral phenotypes. The many facets that give rise to the clinical phenotype, and the complexity of their interactions, have been discussed previously [1-3]. Partially clinically relevant frameworks have been outlined, such as cognitive ability causally determining the behavioral phenotype [4-6], with similar explanations for the causative effects of some environmental agents [2, 7]. However, they have been theoretical in nature, without operationalization allowing for clinical implementation or disorder modelling.

The absence of a concrete theoretical framework may explain the perceived heterogeneity of these disorders and the difficulty in explaining findings such as biased sex ratios, the multitude of environmental agents acting as risk factors, frequent findings of immune and autonomic dysregulation, as well as clinical findings regarding “loss” of diagnosis, optimal outcome prediction, atypical acquisition and presentation of disorder, and the patterns and rates of co-occurring NDDs.

This paper presents a deconstruction of the pathogenesis of NDDs into three interacting factors: genetic susceptibility, cognitive compensation, and risk factors. They are furthermore operationalized, and methods for their clinical quantification are outlined, which can aid clinicians’ evaluations, possibly allowing for faster and cheaper diagnostics. Clinical evaluations entail neuropsychological testing, identification of disorder-specific behaviors (symptoms), as well as identification of severe and explicit insults/diseases, but not implicit and weakly contributing ones. The framework expands upon previously proposed hypotheses, and, in so doing, provides a coherent explanatory model that is practically useful and accounts for several crucial issues, while underscoring the importance of always considering the contributions of all three mechanisms for each individual, not only in severe cases. Potential avenues for future research and empirical validation of the framework are presented. The framework will be presented through the prism of autism, but generalizes to other NDDs.

2. Introducing the pathogenetic triad

The framework includes three features that interact to determine the observable behavioral phenotype, which in some cases will be identified as necessitating a clinical diagnosis:

- 1) *Genetic susceptibility is operationalized through the Disorder Personality Type (DPT)* – The DPT represents the genetic architecture and endophenotype which is specific for each disorder, and expresses itself behaviorally as a spectrum of behaviors typical for the given disorder, with the disorder being over-represented at the upper end of that spectrum
- 2) *Cognitive compensation is operationalized through Cognitive Capacity (CC)* – CC represents the ability of an individual to recognize, respond to, and learn from environmental cues and demands, as well as cope with the issues arising from a strong endophenotype and its associated behavioral phenotype
- 3) *Risk factors are operationalized through the Neuropathological Burden (NB)* – Risk factors undermine brain development and function. The degree to which that occurs depends on the individual’s ability to alleviate their impact through proper immune function and physiological regulation. The NB represents the emergent effect from the interaction between insults and defensive mechanisms

Figure 1 illustrates the triad and how its constituent parts interact to cause the behavioral phenotype that we associate with a given NDD. Table 1 illustrates the framework by presenting the triad and how it can be operationalized and quantified.

Figure 1. A schematic detailing the pathogenic triad underlying the clinical expression of neurodevelopmental disorders. Red and blue boxes represent contributing, and protective factors respectively. Red arrows indicate a negative/inhibitory relationship, and blue arrows indicate a positive/contributory relationship. Since studies investigating the direct effects of biological risk factors in the endophenotype are lacking, one cannot exclude that certain risk factors contribute to the endophenotype, such as when they affect similar neurobiological pathways. Future studies will have to investigate this specifically.

Contributing Factor	Operationalization	Quantification
Genetic Susceptibility	Disorder Personality Type	<i>Personality questionnaires:</i> e.g. Autism Quotient for autism <i>Biological tests:</i> Polygenic score or neurobiomarkers
Cognitive Compensation	Cognitive Capacity	<i>Neuropsychological tests:</i> e.g. Intelligence or Executive Functions
Risk Factors	Neuropathological Burden	<i>Categorical:</i> Insult characteristics <i>Continuous:</i> Heart Rate Variability

Table 1. This table presents the proposed triad for the pathogenesis of neurodevelopmental disorders and outlines methods for the operationalization and quantification of each factor.

3. Genetic susceptibility - The Disorder Personality Type

A high heritability, with polygenic inheritance, is typical for NDDs [8]. The polygenic nature of NDDs predicts that each of them is underlined by a normally distributed neurobiological behavioral and endophenotype, across the population, with the upper range being disproportionately affected by the given NDD. The magnitude of the genetic burden, from common susceptibility variants [9], determines the degree to which each endophenotype, and ultimately also its associated behavioral phenotype [10], is behaviorally expressed. In other words, individuals with a high genetic burden present more frequent and intense behaviors (symptoms) that we associate with a certain diagnosis and are thus more likely to be clinically identified. The genetic susceptibility may be quantified either on the phenotypic level using questionnaires, or on the biological level using polygenic scores or the neuroendophenotype (anatomical and physiological biomarkers).

For autism there is a Broader Autism Phenotype (BAP) which is characterized by issues with social interactions, repetitive behavior, alterations of sensory processing, pragmatic language, and an aloof personality [11], which can be quantified using, among others, the Autism Spectrum Quotient questionnaire [12]. There are several indicators that underscore the importance of the BAP as a core feature of autism with an underlying behavioral phenotype that is shared by individuals with and without a diagnosis: the BAP is normally distributed in the population [13], and there is a correlation between the BAP and the genetic burden of autism [14]; relatives with a high BAP have a neurobiology and cognitive phenotype intermediate that of probands and typically developing controls [15, 16]; the BAP of relatives predicts the severity of the disorder in diagnosed probands [17], and their own probability of having a diagnosis [18]. These factors suggest an underlying personality inventory that is normally distributed in the population, where some individuals have a strong behavioral phenotype, and may be considered “odd”, but are otherwise well-functioning.

The behaviors that stem from a given endophenotype may, when intense enough, present the individual with problems. This represents a “first hit” for the development of a given disorder. For example, individuals with schizotypal tendencies are generally more suspicious than those without, with stronger tendencies bordering on paranoia, potentially affecting an individuals’ ability to interact socially and otherwise. What causes some individuals with a high genetic susceptibility to develop a maladaptive phenotype that warrants a clinical diagnosis?

4. Cognitive compensation - Cognitive Capacity

CC represents the cognitive functions, such as intelligence and executive function, that allow the individual to compensate for potential behavioral problems. It is not hard to intuit that individuals with a poor CC will have greater difficulties compensating for issues arising from a strong behavioral phenotype, and that their difficulties persist over time. For example, an individual with autism and sensory sensitivity may become distracted in a crowded environment. However, having a high working memory may allow that person to maintain its thought processes, while simultaneously processing the large number of incoming visual stimuli, allowing continued social interaction despite being in a distracting environment.

The behavioral phenotype in individuals with a poor CC becomes thus more pronounced, debilitating, and easily identified, warranting clinical attention and leading to a diagnosis. For adaptive responses to complex environmental demands (such as a social interaction, as opposed to reacting to a sound), the higher cognitive functions (HCF) are instrumental [19]. An inferior CC in general, and impaired HCFs in particular, are frequent findings in NDDs [20, 21] and have been shown to influence both the clinical presentation and severity of disorders [22]. Given the association between NDDs and intellectual disability, it is likely that a high CC causally modulates the observed phenotype by ameliorating behavioral issues that arise from a high genetic susceptibility [5].

As with the disorder endophenotype, CC is highly heritable [23], and they seem to be inherited separately. For example, relatives with normal or high CC tend to have probands diagnosed with high-functioning autism, while those with low CC have probands with lower-functioning and more severe autism [24, 25]. Also, measures of CC negatively correlate with the number of expressed autistic traits [26], risk of diagnosis [27], and the number of comorbidities [28]. A possible explanation for the finding of low intelligence and executive functions in NDDs is that the CC is left-shifted due to a clinical ascertainment bias [4], and that this represents a “second hit” for expressing a maladaptive behavioral phenotype that warrants a diagnosis.

The CC is operationalized as an umbrella term for cognitive domains – such as intelligence and executive functions – that have protective effects on various aspects of behavior in general, and the disorder phenotype in particular. CC is purposely vaguely defined in this framework since the importance of different subdomains varies depending on the NDD in question (such as verbal intelligence being a greater predictor of optimal outcome than spatial intelligence in autism [29], due to its disproportionate effect on social communication difficulties). The global effect of CC is conceptualized within the framework, but it is the task of neuropsychological research to investigate the clinical effects of specific subdomains in different NDDs. In testing the framework, measures such as IQ or working memory may be used. Development of a (disorder-specific) compounded index of several measures, through modelling, will likely improve the quantification and clinical predictive value of CC.

Figure 2 illustrates the association between the behavioral phenotype for a given disorder and the CC, and how they together determine the clinically observed behavioral phenotype. Plotting data from population-based studies will allow for empirical validation of the model and its predictive value regarding disorder severity, probability of diagnosis, and diagnostic stability.

Figure 2 Illustration of the association between Cognitive Capacity and the behavioral phenotype for a given Neurodevelopmental Disorder; for autism one could plot working memory against the Autism Quotient score. The diagnostic threshold is represented by a fuzzy demarcation due to the difficulty in assigning a diagnosis to borderline cases, and resulting low agreement across neuropsychiatric evaluators. The slope and shape of the

threshold are yet to be determined, for which population-based studies will be instrumental. A greater distance to the diagnostic threshold is associated with a more confident diagnosis (or lack thereof) due to a more typical behavioral phenotype (corresponding either to a neurotypical phenotype, or that which is associated with a given disorder), and thus a greater diagnostic stability over time. The shading under the threshold represents the severity of the disorder, the intensity of the observable phenotype, and the probability of attracting clinical attention and thus receiving a diagnosis.

5. Risk factors – the Neuropathological Burden

There are countless etiological risk factors, both exogenous and endogenous, for NDDs (see table 2). Despite the large number of widely different etiologies impacting different pathways, one or a few common pathophysiological mechanisms likely exist. The fact that etiologies are both non-specific for a given NDD, and that they never account for a substantial majority of cases, may indicate that they have a primary effect on a modulating factor, such as CC, rather than the disorder per se. The etiological overlap between different NDDs extends also to the neurotypical population by affecting brain and CC development in general (table 2). All somatic insults activate the hypothalamic-pituitary-adrenal axis and immune system, divert resources from growth and development to repair and defense, and secondarily affect brain development. An etiological pathway that converges on neurodevelopmental inhibition, where risk factors disinhibit maladaptive behavioral phenotypes by undermining brain and CC development, would explain the overlap of etiologies between different NDDs and low CC across the population.

As mentioned, the HCFs are disproportionately important for cognitive compensation. Compared with the lower cognitive functions, the neurobiological underpinning of HCFs rests on larger brain areas and consist of more complex neural networks. This offers more potential vantage points for perturbations and explains their disproportionate impairment in the face of neurodevelopmental insults, and why even low-grade insults need to be taken into consideration within a model of NDDs. Not only strong and explicit neurological insults, but also multiple small normally distributed ones have downstream effects across the hierarchies of neural processing. There are parallels between lower/higher cognitive functions and gross/fine motor coordination in terms of neurophysiology and sensitivity to insults, indicating why coordination problems are common in patient populations, and why control of the effect of intelligence (both are affected by a common confounder, namely the NB) removes that effect [30].

Rare susceptibility variants and genetic syndromes constitute a disease burden that causes NDDs by negatively influencing CC (while also inducing heterogeneity through specific endophenotypes). Studies corroborate this conclusion by showing that rare variants are associated with lower CC [9], and that low CC is associated with risk of NDDs in genetic syndromes [31], such as individuals with Fragile X and Down Syndromes with lower CC being more likely to be diagnosed with autism than those with higher CC.

Neuropathological insults (see table 3 for operationalization) interact with immune and autonomic function (figure 3) to determine their ultimate effect on brain development. The resulting effect, which is largely normally distributed, is denoted as the NB, where an increased NB leads to a decrease in CC, in particular for HCFs. This subsequently lowers the threshold at which each disorder endophenotype causes a maladaptive behavioral phenotype, and a NDD becomes clinically identifiable and fulfills diagnostic criteria.

Insult (NB)	NDD	CC
Malnutrition Excess/deficit: caloric, vitamin, metal, iodine	Caloric: [1], [2], [4], [7], [8], [9], [10], [29] Vitamin: [3], [29], [30] Metal: [4] Iodine: [5], [6]	Caloric: [11], [14] Vitamin: [15], [16], [17] Metal: [4] Iodine: [12], [13]
Infection / Neuroinflammation Prenatal infection, maternal immune activation	Infection: [8], [9], [23], [24], [29], [30], [32] Immune disturbance: [4], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [30], [31], [33], [34]	Infection: [35], [36], [37], [38], [39], [40] Immune disturbance: [36], [37], [39], [40]
Pre-/postnatal stress Maternal pregnancy-related stress	[9], [10], [30], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [80]	[36], [51], [52], [53], [54], [55]
Obstetric complications Pre- and perinatal complications, prematurity	[8], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65]	[61], [66], [67], [68], [69], [70], [71]
Pre-/postnatal toxins Exposure to medicine, metals, chemicals, alcohol...	Medicine: [4], [72], [73], [74], [75], [76], [77] Metal/chemical: [4], [8], [9], [79], [81], [83] Air pollution/smoking: [29], [47], [78], [80], [81], [82]	Medicine: [84], [85], [86], [87], [88] Metal/chemical: [82], [94] Air pollution/smoking: [82], [83], [89], [90], [91], [92], [93]
Somatic comorbidity Maternal non-psychiatric disorder	Autoimmune: [20], [21], [22], [26], [29], [95], [96], [97], [102] Endocrine: [98], [99], [100], [101], [103], [104], [105], [106]	Autoimmune: [111], [112], [113], [114], [115] Endocrine: [107], [108], [109], [110], [116]
Mechanical trauma Traumatic brain injury	[117], [118], [119], [120], [121], [122], [123], [124], [125], [126]	[119], [127], [128], [129], [130], [131]

Table 2. This table presents several of the environmental risk factors that have been implicated in causing Neurodevelopmental Disorders (NDD). It also shows that those agents have been shown to negatively affect Cognitive Capacity (CC) in the neurotypical population. The non-specificity and overlap of etiologies hints at a common pathway for neuropathological insults, with CC being a possible modulating factor for the expression of NDDs. These etiologies all negatively influence brain and cognitive development, which causes individuals with a predisposition for a certain NDD (through the presence of a strong endophenotype) to develop and express its clinical phenotype. This non-exhaustive list has preferentially included reviews and collections of references with a focus on pregnancy-related and early postnatal factors, which can be thought to have the greatest influence and downstream effects on brain development. See supplementary material 1 for references. NB = Neuropathological Burden.

The negative effects from risk factors on CC does not exclude a specific effect also on NDD pathophysiology (figure 1, arrow between NB and disorder endophenotype); there is likely an overlap of physiological pathways between NDDs and CC development, such as neuroinflammation impairing synaptic function, which is implicated in both autism [32] and CC [33]. Insults that affect CC pathways would lead to downward individual movement on the Y-axis in figure 2, and those that directly affect the disorder endophenotypes would move the diagnostic threshold upward on the same axis. Given that some insults are disproportionately associated with particular NDDs, outlining the characteristics of neurodevelopmental insults may offer explanations for some discrepancies between NDDs, such as epilepsy being disproportionately associated with autism compared with other NDDs. For example, a lower threshold for neural activation in epilepsy leads to alterations in synaptic budding and pruning, with resulting changes in connectivity, which are frequently identified specific mechanisms in autism, but not the pathophysiology associated with attention-deficit/hyperactivity disorder (ADHD).

Heterogeneity of NDDs is a hot topic in the literature, and efforts for achieving stratification have intensified. Biological insults cause distinct neurobiological endophenotypes, which may simply be additive with the disorder endophenotypes. Thus, a possible method for categorical stratification of NDDs is according to the characteristics of the insults (see table 3). Some insults are explicit, allowing for a-priori stratification of research subjects based on expected effects on measured outcomes, such as stratifying for epileptic activity when

performing studies on connectivity in autism. Others are implicit, and will be harder to use for stratification, such as low-level exposure to environmental pollutants. Attempts at stratification according to types of somatic insults have successfully increased statistical power and sample homogeneity [34].

Insult characteristics	Effect on NB	Examples
Magnitude	Greater insult magnitude results in higher NB	Greater neuroinflammation or exposure to toxins causes greater impairment of CC and higher risk for a NDD
Timing	Dependent on developmental time-course of affected physiological pathway	Disruption is greater for a developing neurobiological structure than a mature one; e.g. inhibitors of neuronal migration are more detrimental during times of migration
Brain-specificity	Insults more specifically impacting the brain result in higher NB	Infection and trauma of the brain are more disruptive for brain development than peripheral infection and trauma; e.g. herpetic encephalitis compared with herpes zoster.
NDD-specificity	Insults more specifically impacting key physiological pathways for given a NDD result in a higher NB for that NDD	Autism is more likely to result from disruption of synaptic function than that of long-term potentiation/memory, and from that of the limbic cortex rather than the motor cortex

Table 3. There are several characteristics of neuropathological insults that determine what effect they ultimately have on brain development and the risk of developing a Neurodevelopmental Disorder (NDD). The effects of these characteristics are outlined in the table. All somatic insults result in variable degrees of immune activation and reallocation of resources from growth and development to repair and defense. Individual insulting agents affect specific neurobiological aspects during development, which causes different physiological and anatomical endophenotypes. Thus, the insults underlying the Neuropathological Burden (NB) are a possible candidate for explaining the heterogeneity in NDDs, and represent a potential avenue for stratification through the categorization of insults. CC = Cognitive Capacity.

There is an obvious interplay between biological insults and defensive mechanisms of the body (figure 3). Immune function and autonomic regulation, both with strong genetic underpinnings, have the potential to either alleviate or exacerbate the effects of insults (i.e. the resulting NB from a given insult differs), as well as induce insults of their own (e.g. autoimmune-mediated neuroinflammation or maternal immune activation during pregnancy [35]).

Many studies indicate abnormal, or at least altered, immune function in NDDs, which may represent suboptimal function or immune induction by unidentified risk factors. Their frequent presence in clinical populations may be due to a clinical ascertainment bias rather than being a core component of the NDDs themselves. Individuals with immune function alterations may be less able to cope with biological insults, increasing the negative impact such insults have on the development of compensatory cognitive capacities, ultimately leading to a disinhibition of a maladaptive behavioral phenotype. Which disorder phenotype, and how many, ultimately get expressed and warrant a diagnosis depends on the individual profile of genetic susceptibilities and endophenotypes.

Further implicating immune dysfunction as a modulating feature is the frequent finding of autonomic dysfunction, which is instrumental for proper immune functioning and allocation of resources during disease and development. Heart rate variability (HRV), an indicator of autonomic flexibility, is low in many NDDs [36, 37] and relates to inflammatory markers [36],

hypothalamic-pituitary-adrenal axis activation [36], and low intellectual ability [36]. A flexible autonomic nervous system allows the individual to biologically cope with insults in a timely manner. Interestingly, prenatal HRV is a better predictor of social cognition in adulthood than birth weight, medical comorbidities, or socio-economic status [38], which could signify that HRV mediates the effect between insults and outcome, and determines adult morbidity and adaptive functioning. Since HRV decreases in response to disease, and is predictive of greater morbidity following disease [39], it may act as an indicator of suboptimal autonomic and immune functioning that increases the NB, causing neurodevelopmental inhibition. Future studies will elucidate what role HRV plays in relation to NDD development, whether it modulates adaptive ability in the face of an insulting agent, is a measure of previous insults, or both. Rather than quantifying the NB categorically through insult characteristics, the HRV could represent a candidate for continuous estimation of the NB.

Figure 3. Illustration of the interplay between neurodevelopmental insults and the immune system in causing an impaired Cognitive Capacity (CC), which increases the risk of Neurodevelopmental Disorders (NDD). (1) An insult can directly increase risk for a NDD, through specific NDD pathways or by impairing CC development. Likewise, having a NDD or low CC can increase exposure to certain insults, leading to a bidirectional interaction. (2) Interaction between the insulting agent and the body's immune system; a neuropathological insult can both cause an immune response (either directly causing neuroinflammation through microglial activation, or indirectly through induction by somatically derived immunomodulators such as cytokines) and be a result of one (autoimmunity). Thus, immune activation affects brain development and can be either primary (autoimmune-generated neuroinflammation) or secondary (a result of immune activation by an insult). (3) Autonomic regulation reciprocally modulates immune function.

6. Conclusion, implications and testable postulates

In summary, the polygenic risk for a given disorder, through its effect on the endophenotype, determines the degree to which disorder-specific behaviors are expressed. Those behaviors are inherited separately from the CC, such that individuals can have a strong phenotype and a low CC which attracts clinical attention, while those with high CC either go undiagnosed or receive a “high-functioning” label. That is, the CC causally influences the behavioral phenotype, leading to a clinical ascertainment bias in those with low CC.

Since neurodevelopmental insults both increase the risk of NDDs and decrease CC, and the CC is causal for that risk, it is likely that biological insults modulate risk of diagnosis through their effects on CC. Dysregulated immune and autonomic function increase the debilitating effects from such insults, which decreases cognitive compensatory ability and increases diagnostic probability by disinhibiting a maladaptive behavioral phenotype. These effects also induce a clinical ascertainment bias, explaining the frequent findings of immune and autonomic dysfunction in patient cohorts. These ascertainment biases may underlie the perceived heterogeneity of NDDs; low CC, and autonomic and immune dysfunction are not core features of NDDs, but increase the risk of showing maladaptive behaviors and getting clinical attention. Stratification according to insult type and characteristics may increase homogeneity. Finally, the implementation of HRV may allow for estimation of the longitudinal effects of brain development by biological insults, not only for strong, clinically identifiable insults, but also for the multitude of normally distributed weak insults that one is exposed to across development.

The presented framework fits well with existing literature and outlines a coherent model for the many disparate findings regarding intellectual ability, etiologies, immune disturbances, and autonomic alterations:

- It explains the rate and patterns of comorbidities. There is an increased rate of co-occurring NDDs in individuals with a poor CC and high NB, since each behavioral phenotype is disinhibited at a lower threshold. The patterns of comorbidities are determined by each individual's profile regarding disorder behavioral and endophenotypes; individuals with an increased polygenic burden for autism and ADHD, but lower for schizophrenia, will have a higher likelihood of receiving the first two diagnoses following a neuropsychiatric evaluation. Conversely, receiving a diagnosis of intellectual dysfunction indicates a low polygenic burden for all NDDs, but a high burden for low CC and/or dysfunction regarding immune/autonomic functioning.
- The substantial heritability of all three factors of the triad explains the familial clustering of both single disorders (inherited strong genetic susceptibility for that disorder), and when multiple disorders are present (either an inherited poor CC and immune/autonomic dysfunction, and/or the presence of a strong genetic susceptibility for several disorders). Simplex families (only one diagnosed individual) likely have a high genetic susceptibility for a given disorder and a relatively high CC, but with a serendipitous NB (such as maternal immune activation during pregnancy due to a sporadic infection). Multiplex families, on the other hand, likely have a genetic architecture associated with lower CC and autonomic/immune dysfunction.
- It proposes a rational way of stratification, where homogeneity may be approached through stratification according to insult types and characteristics.
- It provides a clinically relevant explanation for the acquired phenotypes in adulthood, of which there have been several published case studies (such as [40]). For example, an autistic phenotype may be observed following a drop in CC relative to the BAP from damage to either core symptom areas, such as theory of mind, or protective domains, such as the frontal lobe.
- It also offers an explanation for the finding of “loss” of diagnosis; individuals with a low distance to the diagnostic threshold are more likely to be judged to be on the other side of the diagnostic threshold by another clinical observer, as well as being more likely to move across the threshold through adolescence (due to the delayed myelination of the frontal lobes, or increased environmental and societal demands). Loss of diagnosis has been termed optimal outcome, and has been found to occur more often in individuals with high CC. This can be explained through the framework by the higher relative proportion of individuals close to the diagnostic threshold among those with a high CC (top right under threshold, figure 2).
- Unequal prevalence between the sexes may be explained by differences in all three aspects of the triad. Regarding autism, females in general show fewer autistic-like traits [12, 13]; they have superior social cognition [41] which acts as a compensatory mechanism for social difficulties; and they have a lower biological vulnerability [42], and thus a lower NB, irrespective of insult intensity.

From a clinical point of view, lumping disorders under a common umbrella [43] makes sense in terms of treatment and prognosis since the patient populations will share a low CC and high NB due to a clinical ascertainment bias. However, from a research perspective, to achieve homogeneity one needs to separate the clinical syndrome from the neurobiological entity, which is but one contributory factor for a clinical diagnosis. It should be noted that the presented triad

may also constitute a framework for personality disorders, although the biological aspects are likely more subtle.

Novel ideas presented in this framework include that the biological risk factors are associated with NDDs largely through their modulating effect on cognitive compensatory ability, and potentially partially through direct effects on the endophenotype early in development. These effects can be tested, and the relative contributions for each pathway can be determined. The fact that a majority of clinical patients have one or more associated biological alterations (identified risk factors, immune dysfunction, autonomic dysfunction) is likely due to their negative effects on cognitive and physiological compensatory mechanisms, causing a disinhibition of the clinical phenotype and a clinical ascertainment bias. Thus, they are likely not part of the underlying disorder entities themselves, but only of the clinical syndromes that are being observed and diagnosed. Finally, HRV as a measure of autonomic function is tentatively introduced as a quantifiable variable for longitudinal modulation of neural development and may indicate an individual's cumulative exposure to risk factors.

Several questions need to be answered in future studies; which factors affect the endophenotype and what are their neurobiological underpinnings; which CC domains are important for adaptive functioning and how do they interact with specific disorder phenotypes; which insults increase risk the most for each disorder and how; how do the insults interact with the endophenotype and CC; can we identify, predict, and prevent these insults?

There are several potential avenues for testing the premises of the hypothesis. One is to perform longitudinal and transgenerational studies investigating the inheritance pattern and predictive power of the triad factors when jointly considered. Population-based data can be plotted similar to figure 2, but on three axes, to empirically validate questions surrounding the sex ratio, “loss” of diagnosis, timing of gain of diagnosis, optimal outcome, rates of comorbidities, and relationship between disorder severity and distance to the diagnostic threshold (according to points presented above). From this framework it follows that the residual for the regression between the Autism Quotient, HRV and working memory will be related to the probability and severity of autism, and that it may be used to predict diagnostic status with high accuracy. Finally, stratification according to insult characteristics may increase homogeneity and statistical power, lending support to the framework.

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