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The neurodevelopmental continuum towards a neurodevelopmental gradient hypothesis

Summary

In contrast to the categorical approach of the current nosographic system, in the last decades increasing literature is suggesting that psychiatric disorders may be better conceptualized as a continuum, which would feature as a common basis a neurodevelopmental alteration. The “neurodevelopmental continuum” (NC) is a theoretical framework supported by several empirical evidences in multiple fields of research. The conceptual core of this model is that an alteration in brain development, the expression of which would be determined by the intertwined relationships between genetic and environmental factors, may constitute the common underpinning of different kinds of mental disorders. Moreover, the NC theory also implies that psychiatric conditions could be placed along a gradient, where autism spectrum disorder (ASD) with intellectual disabilities would be the most severe expression of an alteration of the “social brain development”, followed by other DSM-5 neurodevelopmental phenotypes characterized by a milder impairment. This model would subsequently include, along a decreasing neurodevelopmental gradient, other psychiatric conditions such as schizophrenia and mood disorders as well as eating and anxiety disorders, encompassing also non-psychopathological personality traits. From a cognitive point of view, the link between neurodevelopmental alterations and vulnerability towards psychopathology could be identified in an impairment of the proprioceptive experience and of the interoceptive inference, which would prevent the patient to properly define his own subjectivity and to adequately place him-self in the relational space. The conceptual framework proposed here may allow significant changes in both research and clinical settings, eventually leading to improve therapeutic and prevention strategies.

Key words

Neurodevelopment • Autism • DSM-5 • Dimensional approach • Comorbidity

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Classification of neurodevelopmental disorders in DSM-5

The fifth edition of the Diagnostic and statistical manual of mental disorder (DSM-5) defines “Neurodevelopmental disorders” (ND) as “[...] a group of conditions with onset in the developmental period. The disorders typically manifest early in development, often before the child enters grade school, and are characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning. The range of developmental deficits varies from very specific limitations of learning or control of executive functions to global impairments of social skills or intelligence [...]”¹.

This category in DSM-5 includes:

- intellectual disabilities;
- communication disorders;
- autism spectrum disorder (ASD);
- attention-deficit/hyperactivity disorder (ADHD);
- specific learning disorders;
- motor disorders (among them: “Tic disorders” such as “Tourette’s disorder”).

However, focusing on features like symptomatological severity, and overall cognitive functionality and adaptability, we may re-think the whole ND cate-

gorization as a psychopathological continuum, where ASD with intellectual disabilities is the most severe expression of an alteration of the “social brain development”². Subsequently, the other phenotypes are characterized by a milder impairment in social communication and interaction, reflecting an intermediate impact on the ability of the new born to define his own subjectivity. A task which may be summarized as the possibility to say: “I am”. That is to say, the ability to reach a valid auto-representation and to develop an adequate theory of mind³. This is a task of utmost complexity, involving all those aspects that contribute to the ontogenesis of the Self in its subjective time and relational space. For this purpose, it is needed:

1. Fully functioning coenesthetic perception: it will allow the subject to build the experience of feeling his own body in an integrative fashion, perceiving it as one global entity, functioning under subjective control. The experience can be summarized as “I feel my own body”⁴;
2. The ability to develop cognitive maps, integrating the sensorial information about the world with past experience and with the bodily representation in time and space. This includes a perceptive cycle that allow the subject “to see” as something different from the experience of his own body⁵;
3. An inner representation of the ways in which others might see the subject: “to be seen”. The cognitive ability “to be seen” includes several orders of consequences. First of all, there must be some kind of other object able to “see”. Some kind of intentionality (thus some kind of subjectivity) must be recognized in that object. These characteristics transforms the “watching” object in a proper “other subject” different from the subject but with comparable interior states. This last feature, extremely complex, underlies the appearance, in the child, of the ability to lie^{3,4,5}.

Each alteration of these features may lead to a severe impairment in the way a subject perceives its own body and build the experience of the world, including that of its own position in it^{4,5}. We may suppose that a severe distortion in the development of these fundamental functions of the brain would result in the conditions listed under the “ND” category of DSM-5. However, milder alterations of the same functions may not produce detectable symptoms during childhood, remaining almost silent, or at least not leading to full-blown clinical manifestations. Despite that, they may actually result in other kinds of expressions, such as milder cognitive impairment, odd thinking or bizarre behaviours, neurotic traits, relational abnormalities^{2,5,6}. These features, when requiring clinical attention, may appear as a full-fledged anxiety disorder, such as social anxiety, specific phobias or panic attacks⁶. In this framework, it is noteworthy that social anxiety, as autistic-like ND, is a disorder which features, from a clinical and neurobiological point of view, an impairment in social brain⁷. Some literature has

also highlighted how social anxiety disorder may mask autistic traits (AT) among females⁶. Mild alterations in neurodevelopment may also lead to an enhanced self-focus and to mental rumination, resulting in intrusive thinking and cognitive inflexibility about body health or shape: this is in line with the literature that is suggesting a significant overlap between AT and eating disorders⁸, as well as hypochondria or dysmophophobia⁹. Sometimes an association with neurological soft-signs can be also detectable¹⁰. Recently a growing body of studies stressed the importance of investigating mild symptoms of neurodevelopmental alterations, such as AT, due to their possible role in promoting different kinds of psychiatric disorders, including suicidal ideation and behaviours¹¹⁻¹⁴. These autistic-like mild and atypical manifestations, behavioral traits and personality characteristics, seem to be distributed along the same continuum which includes, at its extreme end, the “ND” category of DSM-5⁶.

In the last decades several psychometric scales have been developed in order to assess AT⁶. These instruments show how AT may cross the border of ASD, showing overlapping features with other ND, as well as with adult psychoses (schizophrenia and bipolar disorders) and eating disorders⁶. AT are also considered a significant vulnerability factor towards life events^{6,11}. This data is of specific interest considering the well-known role of traumatic experiences in precipitating the onset of psychopathology^{6,15,16}, leading to hypothesize interlaced relationships between AT and post-traumatic symptoms in shaping psychopathological trajectories^{6,11}.

From the “Neurodevelopmental Continuum” towards a “Neurodevelopmental gradient”

Since the 70's, the conceptual framework in which the DSMs have been developed is that each clinically defined psychiatric disease should have a discrete etiological basis. However, in the last decades increasing literature is suggesting that psychiatric disorders can be better conceptualized as a “neurodevelopmental continuum” (NC)¹⁶. According to this model, similar kinds of alterations, linked to neurodevelopment, may lead to several different functional outcomes and phenotypic expressions. Such different trajectories seem to be related to both specific genetic characteristics and possible environmental influences, as well as to the timing of expression in the lifespan⁶. The NC is a theoretical framework supported by several empirical evidences in multiple fields of research^{2,6}. The conceptual core of the NC model is that an alteration in brain development, determined by the intertwined relationships between genetic and environmental factors, may constitute the common underpinning of many (eventually, all) mental disorders^{2,6}.

Moreover, the NC theory also implies that psychiatric disorders could be placed along a gradient of decreasing

neurodevelopmental impairment. A possible model for this gradient could be understood in these terms ²⁶:

- ASD with strong cognitive deficits (Kanner's type);
- ASD without mild/no cognitive deficits (Asperger's type);
- ADHD;
- intellectual disabilities;
- schizophrenia;
- eating disorders;
- bipolar disorders;
- anxiety disorders;
- vulnerability to traumatic experiences.

According to this hypothesis, the concept of ND should be rethought, in order to include also functional psychoses (schizophrenia and bipolar disorders), and to be considered as a predisposing factor which may open the way to the onset of several other disorders, such as eating or anxiety disorders, as well as featuring a higher vulnerability to traumatic experiences⁶. It is noteworthy that in this model specific attention is paid to the expression timing of the above mentioned disorders, which should be considered within a dimensional approach. The risk for developing clinical manifestations is not homogeneous across lifetime, featuring critical periods associated to both neurobiological and environmental factors, such as life events, but also to age-related and other subject-specific conditions. E.g., a psychotic break that happens in late childhood it is different from one occurring in adult life, in both terms of possible precipitating factors and possible impacts on the personality structure ⁶.

Neurodevelopmental disorders beyond the borders of DSM-5

As reported above, a mild alteration in neurodevelopment may prevent the subject from building an appropriate self-representation and a satisfying relational life, which may lead to different kinds of clinical expressions ^{2 4 5 6}. However, generally the onset of clinical manifestations in these cases does not occur in childhood, but in adolescence, when the subject must face new challenges, with a significant impact on the global adjustment ⁶. The scientific and cultural framework within we may investigate the psychogenesis of the most dramatic psychiatric disorders, such as schizophrenia, bipolar disorders but also eating disorders, should focus on the role of a deficit in the proprioceptive experience, such as deficits in "feeling" our own body and its relationship with external space and past events ⁴. For example, in eating disorders and self-injuring behaviours we may hypothesize an abnormal perception of patient's own body, including an altered reactivity towards pain ¹⁷. In particular, in line with recent hypotheses from computational psychiatry, an alteration of the interoceptive system, with an impairment of the ability of inferring

one self's states (as if they were of someone else) may be a common cognitive feature of apparently different disorders such as hypochondria or dysmorphophobia ⁴.

According to the current theoretical and nosographic framework, the clinical expression of ND is considered firmly separated from the major clinical manifestations typical of adult life. The separation could be related to age of onset (first years of life vs adolescence or youth). However, the most striking differences lie at the level of clinical presentation: symptoms such as delusions and hallucinations are usually described in adulthood, while they are not frequent in childhood (and in particular, they are not strictly included among the manifestations of ND as reported in DSM-5). It is specifically the primacy of these psychiatric symptoms that draws a line between ND and major psychoses such as schizophrenia or mood disorders. However, this marked distinction may fade when considering the shared presence, in the above mentioned conditions, of ^{10 18 19}:

- cognitive impairment, which is present before (and after) psychotic breakdown;
 - neurodevelopmental delays;
 - neurological soft signs;
 - motor abnormalities;
 - a long list of supposed "comorbidities" with neurotic symptoms and psychopathic traits;
 - overlapping environmental (especially when related with early brain development) and genetic risk factors.
- On the other hand, the possible trajectories of the NC are not limited to full-blown psychiatric conditions ⁶. From a broader point of view, they may converge in ^{6 11}:
- A condition of significantly higher vulnerability towards the development of full-threshold psychiatric symptoms;
 - A tendency to show greater difficulties in coping with traumatic experiences, to the point that almost all life experiences would be, in some way, "traumatic". This feature may be considered as the expression of an inability to face the experience of the world, and properly adjust to it, eventually reorganizing the perception of the personal world.

The environmental factors which may open the way towards a full-blown psychosis could be associated to the challenges of entering adult life. These latter may feature the confrontation with new kinds of intimate relationships, such as the sexual ones, the adjustment to work environment, the necessity to reach higher independence in daily life ⁶. A psychotic episode could precipitate the premorbid condition of vulnerability and disrupt the previous functional adjustment (which was unstable from the beginning), promoting a further disorganization of the neurobiological asset. Psychotic symptoms may persist or not as residual symptoms after recovery; nevertheless they often lead to a worsening of the neurobiological and social functioning ¹⁸.

Concluding remarks

The conceptual framework here proposed may lead to significant changes in both research and clinical settings, including therapeutic and prevention strategies. The main assumption of this model lies in the recognition of several perceptive, cognitive and motor phenotypes which may co-occur in different clinical populations, with an evolution over anamnestic history. These phenotypes seem to share etiological and pathogenetic mechanisms, while the variables influencing their outcome may be identified in:

- the specific genetic asset of each person;
- the life-long interaction with environmental factors, including therapeutic strategies and the ability of the patient to seek help.

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