Default Mode Network Maturation and Environmental Adversities During Childhood

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Abstract
Default mode network (DMN) plays a central role in cognition and brain disorders. It has been shown that adverse environmental conditions impact neurodevelopment, but how these conditions impact in DMN maturation is still poorly understood. This article reviews representative neuroimaging functional studies addressing the interactions between DMN development and environmental factors, focusing on early life adversities, a critical period for brain changes. Studies focused on this period of life offer a special challenge: to disentangle the neurodevelopmental connectivity changes from those related to environmental conditions. We first summarized the literature on DMN maturation, providing an overview of both typical and atypical development patterns in childhood and early adolescence. Afterward, we focused on DMN changes associated with chronic exposure to environmental adversities during childhood. This summary suggests that changes in DMN development could be a potential allostatic neural feature associated with an embodiment of environmental circumstances. Finally, we discuss about some key methodological issues that should be considered in paradigms addressing environmental adversities and open questions for future investigations.

Keywords
default mode network, connectivity, environmental exposure, typical brain development

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Introduction
The investigation on how environmental conditions impact childhood development and, by extension, burden the later adult life is of fundamental importance. In fact, 13% of the world’s population lives in extreme poverty, with 800 million people living under starving conditions, among other adversities, such as the lack of basic sanitation.1 Neurodevelopmental research has begun to assess differential negative aspects of environmental adversities that children live in poverty face,2,3 like social disparity,4 low socioeconomic status,5 early life stress,6 abuse, neglect,7 witnessing domestic violence or other kinds of negative parental/relative conflicts,8–10 and living in urban environments.11 These studies are related to both acute and chronic exposure on lifespan. These forms of adversity are also associated to many psychiatric disorders, as, for example, those disorders related to acute stress experiences as early life trauma due to child abuse and child neglect or maltreatment and posttraumatic stress disorders;12–16 socioeconomic issues; anxiety and depression disorders;17,18 and schizophrenia.19

It is of special interest to know when, how, and why these environmental adversities could impact neurodevelopment, especially during the different phases of childhood when brain changes are taking place.20 From this perspective, neuroimaging proved to be a useful tool for non-invasive in vivo structural and functional brain

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investigation. Association between environmental conditions and brain structure and function was reported in previous studies. However, only recently, few investigations have explored the influence of these conditions on brain functional connectivity and its developmental trajectory. The analyses of large-scale networks were demonstrated to be a useful framework to comprehend the underlying complexity of multiple brain subsystems not only in the study of cognitive functions but also in mental disorders.

Considering the multiple brain subnetworks, the investigation of the default mode network (DMN) is of special interest given its pivotal role in neuroimaging studies and also in brain disorders. Atypical patterns of DMN connectivity have been associated with a wide range of psychiatric and developmental disorders such as post-traumatic stress disorder, autism, and others. Findings based on clinical samples provided insightful contributions to enhance the comprehension of DMN functioning.

Beyond its attributed role in mental disorders, alterations in DMN activity have also been associated to enduring outcomes by growing up under stressful conditions, according to retrospective reports in adult’s investigations. However, the studies based on developmental samples (i.e., with children and adolescent samples) are still scarce. These samples should be taken in consideration given the changes occurring in this network during development.

In this review, we aim to provide an overview and perspectives of studies on the association between environmental adversities and the DMN maturation. In order to define the scope of this study, it is important to clarify that (i) our main concern was to present representative studies in this topic (and not a systematic review); (ii) since the literature on DMN and psychiatric disorders is massive, and we decided to focus on other issues in this review.

Although the DMN is well-established in adults, the maturation trajectory from childhood to adulthood is still not fully understood. Its maturation occurs mainly in the postnatal period (as it occurs in many other large-scale networks); therefore, it could be potentially influenced by environmental factors during childhood. Actually, only 23% of the functional connectivity within DMN was found heritable. Many studies have suggested that environmental conditions are related to brain structure. However, there are few investigations exploring their associations with changes in functional connectivity.

**Default Mode Network**

The DMN is a group of functionally connected brain regions that exhibit higher levels of activity during rest than during performance of externally oriented cognitive tasks. Moreover, functional connectivity studies showed that the activity of these regions is negatively correlated with the activity of cognitive-control networks. Consequently, DMN has been involved in a variety of high-level functions, such as attention and inhibitory control, social cognition, episodic memory, and self-related processes. There is still a great debate regarding the assignment of these functions although most of them could be interpreted as dimensions of internally focused thoughts.

Altered DMN connectivity related to deficits on those assigned cognitive functions has been described in psychiatric and neurological disorders, such as in psychoses, mood disorders, attention deficit/hyperactivity disorder (ADHD), autism, schizophrenia, bipolar disorder, and others. One potential biological underpinning of DMN deregulations is identified as its orchestrated functioning with cognitive control regions.

The DMN activity is typically suppressed during demanding cognitive tasks directed toward external environment and goal-directed activity and vice-versa. The unbalance between the activity of DMN and cognitive control network (i.e., a disruption in the functional connectivity between regions from these two networks) was related to autism disorder and to ADHD. Besides that, DMN hyperconnectivity was identified in mood disorders such as depression and schizophrenia. Sato et al. and Castellanos et al. reported a decreased functional connectivity between anterior cingulate cortex and DMN regions in adults with ADHD. As mentioned in the Introduction section, the literature of DMN and psychiatric disorders is massive, and we decided to focus on other issues in this review.

**Age-Effect in the DMN: From Childhood to Adolescence**

In the adult brain, DMN nodes consist mainly of the ventral medial prefrontal cortex (vMPFC), dorsal medial prefrontal cortex (dMPFC), lateral temporal cortex (LTC), inferior parietal lobule (IPL), posterior cingulate cortex/retrosplenial (PCC/Rsp), and hippocampal
formation (HF+), which are densely functionally connected to each other within the DMN. This network undergoes a gradual developmental change on maturation. Gao et al.77 and Fransson et al.78 were the first researchers to report the postnatal DMN. The authors describe that full-term babies presented a “proto-default network,” with a resting-state functional connectivity between the medial and lateral parietal cortex but no significant functional connectivity between the medial prefrontal and the temporal cortices.

Gao et al.,77 in a longitudinal study with infants from birth to the second year of life, found similar results to the ones previously described. They report that from birth to 2 weeks old, the DMN presents few connected regions, with additional regions being connected through the following 2 years toward the pattern found in adults (including MPFC, PCC/Rsp, IPL, LTC, and hippocampal regions). They highlight that until the 2 years old, the strongest connection across all brain regions was between PCC and MPFC. Both Gao et al.77 and Fransson et al.78 described a sparse and fragmented connectivity between DMN regions (i.e., weaker internal connectivity). This network immaturity persists until the 7 to 9 years old, at least.47 They speculate that these network changes may be associated to the emerging self-consciousness and self-referential activity, one of most attributed functions to DMN.

From 3 to 5 years, changes were described in relation to the hemispheric dominance in the DMN subsystems. A decreased right hemispheric dominance (between the medial temporal lobe and dMPFC) is observed at age 3, becoming more bilateral at age 5. The stronger interactions between dMPFC and temporal lobe in 5-year-olds support the development of social cognition, possibly as an outcome of environmental adaptation and other complex mental abilities. The network is still primitive in its functional structure when compared to adults.80

According to Fair et al.,47 DMN regions are still sparsely functionally connected until 7 to 9 years old, in which the connections between vMPFC, PCC, and parietal regions are minimal.47 This study highlights that the typical maturation of DMN may reflect a reduction in short-range connections strength and an increasing strength of long-range connectivity between its anterior and posterior regions. Besides, in the early adolescence (13–14 years old), the increasing connectivity within DMN is still an ongoing process.41,81

From 7 to 15 years old, Sato et al.41 showed the strengthening of functional connectivity between anterior–posterior regions (predominantly between the anterior and vMPFC/lateral parietal and Rsp cortices), highlighting that the anterior MPFC is especially sensitive to the maturation process. In a longitudinal study with early adolescents (10–13 aged), Sherman et al.81 found robust connections between MPFC and posterior parietal cortex, and an increased anticorrelation between DMN and central executive networks over development. Both studies described higher hierarchical DMN functional organization and integration between the posterior and anterior modules over development, toward a similar pattern of adults. These changes are accompanied by the developments in social and cognitive domains such as social learning, usually associated with increasingly sensitive to social cues and peers relationships, from family to society.82 Finally, at age 21, it is expected that DMN is fully integrated.83

In summary, these findings suggest that DMN undergoes developmental changes on maturation, reflecting a long-term trajectory from childhood to adulthood. However, the complex interplay between environmental demands and DMN maturation and how these could be related to an atypical or aberrant development pattern remains unclear.95

Environmental Adversities During Childhood and the DMN

It is established that the early onset of mental disorders can be related to atypical neurodevelopment processes,84 which in turn have been impacted by the exposure to environmental conditions.14,85,89 Many studies focused on DMN alterations in adult populations within mental disorders and also in cognitive function.34,86–90 However, few studies explored the potential enduring effects of adverse situations in childhood on the DMN.2,27,28,91

Structural findings have described the impact of early childhood negative environmental experiences on the brain, including affected areas which might be relevant for DMN functioning.2,9,24,25,76,92–94 For example, low family income is correlated with a decreased volume of the left hippocampus, bilateral IPL, insula cortex, inferior frontal gyrus, right occipital, and MPFC.25 These regions are involved in the DMN network functioning and related to various language and executive functions.76

Recently, some studies investigated the associations between adverse environmental factors, such as low socioeconomic status, poverty and other similar material deprivations, and changes in the functional connectivity involving DMN regions.3,28,95 Adults who experienced chronic poverty in childhood exhibited reduced DMN regions connectivity, as well as higher cortisol levels in anticipation of social stress.3

On the other hand, the interplay between adversities and neurodevelopment does not seem to be univocal. In other words, adversities may result in distinct direction of brain connectivity changes. Family environment adversities, such as exposure to parental aggressive behavior/conflict, were associated with hyperconnectivity between the core DMN regions (PCC/anterior MPFC) and the amygdala in children aged 6 to 12 months.28 In this
context, the author interpreted DMN connectivity alterations as a mediator between higher conflict and higher negative emotionality, suggesting resilience or adequate coping with adverse experiences. In a longitudinal study following 65 children from birth to the first year of life, higher levels of income and maternal education were associated with higher within-network connectivity. Similarly, supportive and warmth parental practices have been suggested as a protective buffer against disturbances in the DMN development of children and adolescents. Nevertheless, it is still unknown whether the increased or decreased connectivity might be related to impairment or compensatory mechanism in the network in face of environmental demands.

**Resilience**

We have shown that exposure to environmental adversities is related to neuropathological costs of adaptation to these environmental demands, specifically the potential neural embodiment in DMN. In this case, embodiment refers to the way in which an organism biologically incorporates the world around it, including societal and ecological situations.

When children are chronically exposed to environmental adversities, their allostatic responses can be excessively required through development. This may lead to a load with potentially negative health outcomes through the physiological wear and tear, the so-called allostatic load. Allostatic process is a mechanism to establish a new (allostatic) accommodation when facing a challenge, which results in adaptive shifts in a broad range of physiological systems matching the internal functioning to the environmental demands. Specifically considering the neural systems, some of these adaptive shifts correspond to structural and functional changes in subcortical and cortical brain regions, such as connectivity changes between the amygdala, hypothalamic–pituitary–adrenal (HPA) axis, and DMN connectivity during development. Graham et al. reported that familiar interactions are associated to DMN functional connectivity in children (6–12 months of age). Children exposed to parental aggressive behavior/conflict showed stronger connectivity between the core DMN regions (PCC/anterior MPFC) and amygdala, which were identified as a mediator between higher conflict and higher negative emotionality. In adults, Philip et al. described analogous findings. Those who were exposed to a chronic stressful childhood had similar increased connectivity between MPFC and amygdala and a decreased connectivity within the DMN. These changes could represent a response to the environmental challenges, once they could preserve their mental health and cope adequately.

Eventually, this load potentially increases the risk of developing physical and mental illnesses when the threshold of an individual is exceeded, as we have briefly described in disorders in which DMN is involved. In other words, their allostatic overload could lead to cognitive dysfunctions.

However, despite facing severe adversities in life, such as deprivation or many types of threats, some individuals are still able to maintain good mental and physical health, the so-called resilient. According to Lupien et al., the nature of the stress response elicited in these situations (negative or positive) relates more to the perception and interpretation than to the physical consequences. In this context, we conjecture that the investigation of DMN developing in individuals under these circumstances might be helpful to comprehend how overload and threshold are modulated and related to the resilience capacity.

According to Patriat et al., environmental challenges are processed by DMN through its mediation of information flow between subcortical and cortical regions. The DMN might integrate salient external or internal information with the current affective individual experience and perception. Such an attribution of meaning to personal experiences has been called self-referential activity, an important cognitive function. This function is expected to emerge after the first 12 months of life. Through self-referential activity, individuals label their experiences as negative or positive (producing allostatic overload when they are excessively negative) according to their perceived social standing. Empirical findings suggest that parental relationships modulate these perception, as they have been related to DMN development and since the parents provide the earliest affective experiences of the children.

**Perspectives**

Although it is still not possible to disentangle whether abnormal DMN connectivity is the cause or the outcome of many mental disorders, the few available studies support that stress and environmental adversities are important factors to be considered in the DMN maturation. In this context, it is necessary to achieve a more in-depth understanding of how adverse environmental factors could affect DMN development. The first and most direct association is to account adversities acting as risk factors to the typical DMN connectivity and by extension, playing an important role in mental disorders; the second is to investigate the correlation between resilience and DMN. Regarding future studies, it is recommended some cautionary considerations when framing the environmental adversities.

First, there is a clear challenge in objectively defining what a stressful or an adverse environmental experience is. One possibility is to take into account the biological evidences related to physiological stress responses.
through HPA-axis activity and their possible associations with structural or functional brain alterations. Previous findings in adults have shown that the effects of chronic exposure to stress in MPFC, an important DMN node, are associated with impairments in long-range connectivity across the brain.

Recent empirical findings investigate the possible neurochemical underpinnings of DMN activity, especially focusing on neurotransmitters such as serotonin, glutamate, and gamma-aminobutyric acid and exposure to stress conditions. The potential association between these neurotransmitters and the DMN is still an open question. One point of particular relevance is to understand the mechanisms driving DMN neurochemical modulation in typical development in children and adolescents and the effects of the exposure to adverse life experiences.

Considering the nature of child development, it is important to reinforce the crucial role of longitudinal studies, which might provide more detailed inferences on maturation. This is necessary to evaluate how exposure levels of adversity change across development. It is also important to take into account that there are some limitations of DMN studies in children. It is well-established that head motion may bias inferences on age-effect. Motion artifacts weaken DMN long-range connections and strength short-range connections in visual regions. Both situations require methodological procedures to minimize errors, such as report and account motion in the comparison between individuals or between groups, and volume censoring technique (scrubbing) to identify scans more affected by motion.

It is also necessary to take into account the functional-anatomic heterogeneity since the maturation of DMN is not homogeneous. Individual variability and heterogeneity of functional networks are crucial points to be considered. On the other hand, evidences of environment-gene interactions have identified regularities in neurodevelopmental trajectories of individuals among diverse populations.

Furthermore, most studies are based on time-stationary patterns of functional while time-varying connectivity analyses might be a valuable methodological tool. Indeed, there are evidences that temporal instability exhibited by the functional connectome allows the switch between multiple configurations within a scanning session. Specifically, Chang et al. recommend the study of temporal dynamics between DMN regions, reinforcing that the majority of studies have only tested stationary relationships between resting-state networks, including the study of the variability of the strength of the anticorrelation between DMN and executive control networks. Calhoun et al. proposed the term “chronnectome” to describe these metrics that enable us to have a dynamic view of coupling of time-varying levels of correlated activity between spatial and temporal properties of brain regions.

Since the functional connectivity expresses complex and multivariate features, the use of machine learning methods would be a promising approach. A rising number of studies have used this approach combined with functional connectivity. For example, Dosenbach et al. trained a machine-learning model to make predictions about individuals’ brain maturity across development, achieving an accuracy of 91%.

Second, the evaluation of environmental exposure effects on DMN maturation is important to account for possible variables as confounders or covariates in studies, such as (i) the time when environmental adversities exposure occurs and their duration; (ii) sex differences, since they might be potentially related to differences in perception of stressful events in puberty and adolescence. In a study with 900 children from 0 to 5 years old, Duncan, Brooks-Gunn, and Klebanov found that living in poverty for relatively short periods is less detrimental than longer ones through development. This finding suggests that chronicity effects may lead to different outcomes. Therefore, it is also important to consider that beyond the functional DMN analysis, greater accuracy will be provided about the environmental exposure if researchers also investigate their relationships to behavioral aspects.

Conclusion

In summary, considering that environmental factors have been strongly associated with many psychiatric disorders, further investigation of their relationship with DMN developmental trajectories is of pivotal importance. To set up these paradigms of investigation, it is fundamental to define more accurately the environmental adversities. The better comprehension of these environmental influences on the DMN development should improve mental health knowledge, supporting more adequate decisions in interventions in the social/environmental policies and educational and parental practices.

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