Default mode alterations in posttraumatic stress disorder related to early-life trauma: a developmental perspective

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Introduction

Recently, altered default mode network (DMN) connectivity in individuals with posttraumatic stress disorder (PTSD) has been related to prolonged childhood maltreatment.¹ An emerging body of literature also describes the developmental differentiation of the DMN in healthy children.²⁻⁶ Critically, developmental changes in the DMN may parallel those observed in other associated domains, including self-referential processing, autobiographical memory, prospection and theory of mind, which are thought to rely on many of the same underlying processes and neural substrates implicated in the DMN.⁷ Moreover, deficient DMN connectivity in adults with childhood maltreatment-related PTSD appears similar to patterns of DMN connectivity observed in healthy children aged 7 to 9 years. Here, we propose that early-life trauma may interfere with the developmental trajectory of the DMN and its associated functions.⁸⁻¹¹

Default mode network

Neuroimaging studies suggest that the resting state in humans is characterized by an organized pattern of activity across disparate anatomic regions that is attenuated during goal-oriented mental activity. Among the identified coactivation networks, the so-called default mode network has sparked the most investigations. A recent meta-analysis⁷ has identified various areas as DMN components, including the

posterior cingulate cortex (PCC), anterior cingulate cortex (ACC), middle temporal gyrus, inferior parietal cortex and medial prefrontal cortex (mPFC). It has been hypothesized that the brain maintains the "default mode" in the absence of cognitive demands,¹²⁻¹⁴ possibly to facilitate a state of readiness to respond to environmental changes.¹⁵ Other authors link DMN activity to self-referential processing^{16,17} and the so-called "stream of consciousness," as key DMN regions like the PCC and the mPFC have been shown to subserve introspective mental imagery, self-reflection and self-awareness. By contrast, the inferior lateral parietal cortex has been implicated in embodied cognition.^{8-11,18}

Development of the DMN during the first 12 years of life

Developmental studies have been conducted to map the unfolding of the DMN in the maturing brain. Critically, DMN connectivity could not be fully established in lightly sedated preterm infants³ or in full-term neonates during natural sleep.⁶ Instead, Fransson and colleagues,^{3,6} using an independent component approach, report that coactivation in these samples was confined primarily to anatomically homologous areas and that connectivity between frontal and posterior areas was absent. This lack of anterior-posterior integration is likely due to less well-developed white matter tracts supporting functional connectivity in the anterior-posterior direction in infants.¹⁹ These authors did, however, report

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strong coactivation between the precuneus, the PCC and the bilateral parietal cortex. This may indicate that integration within the DMN is beginning to evolve even at this young age, as the PCC, with its high degree of anatomic and functional connectivity, is known to be a main node of the DMN in adults.¹⁸ It appears that the maturation of the DMN involves a stepwise process of integration. Using an independent component approach, Gao and colleagues⁴ identified 3 independent components in infants as young as 2 weeks involving brain regions that are subsequently integrated into the adult DMN (the precuneus/PCC, the bilateral frontal areas and the mPFC with occipital, parietal and temporal areas). These results replicate Fransson and colleagues³ earlier finding concerning the absence of an anterior-posterior integration between the PCC and the mPFC nodes. By 1 year of age, however, Gao and colleagues⁴ noted that this anterior-posterior integration begins to emerge. At this age, only 2 independent components were identified, spanning 13 brain regions in total, 10 of which were consistent with those observed in adults (including the mPFC, PCC, bilateral lateral temporal cortex [LTC] and bilateral inferior parietal lobule [IPL]). By age 2, these authors still identified 2 independent components spanning 13 anatomic regions consistent with the adult DMN. Six additional regions in the orbitofrontal, superior temporal and parahippocampal gyri, not present in the adult DMN, were also identified in 2-year-old children. Fair and colleagues,² using a modularity approach to functional connectivity, concluded that the DMN architecture in children aged 7–9 years continues to deviate significantly from the adult architecture. Whereas the interhemispheric functional connections between homotopic regions already appear relatively strong in children at that age, the different components of the network are only sparsely connected. It is worth noting that, in particular, the anterior-posterior connections of the ventral mPFC with the PCC and parietal default regions were minimal in the child group. The developmental process in this age group thus is one primarily of integration. By age 9 years, however, Thomason and colleagues⁵ showed that DMN anterior-posterior integration appeared comparable to adult integration levels using a combined methodologic approach of independent component analysis and a deactivation paradigm. They identified the PCC, the parietal cortex and the mPFC as the largest activation clusters and report identical results for the DMN using both methods. In addition to the DMN regions, however, 3 other brain regions (postcentral gyrus, insula and inferior occipital) showed task-induced deactivations. The authors interpret these findings as an indication of greater integration between the DMN and sensory processing regions in children than in adults.

In summary, before age 9 years, the DMN in children is characterized by absent or limited anterior-posterior integration, as indicated by reduced connectivity between the DMN nodes in the PCC and the mPFC. Over the course of development, connectivity is established between disparate anatomic regions, temporarily including regions not part of the adult network, resulting in anterior-posterior integration of the DMN and functional dissociation from other networks. Dis-

ruptions to the DMN across the course of development may in parallel impact emergent capacities dependent on the functionality of this network (see below).

DMN developmental patterns mirror deficiencies in DMN in patients with PTSD

Interestingly, DMN connectivity observed in women with severe chronic PTSD due to prolonged maltreatment during childhood¹ closely paralleled that observed in Fair and colleagues² study of children age 7 to 9 years. The PTSD patients who participated in this study all had a prolonged history of early-life trauma, as shown by high mean scores on all subscales of the Childhood Trauma Questionnaire,²⁰ and had chronic PTSD as assessed with the Clinician-Administered PTSD Scale²¹ (CAPS; mean score 76.9, standard deviation [SD] 19.8). Strikingly, in women with PTSD, the anterior-posterior integration of the DMN was extremely limited. The DMN node in the PCC exhibited coactivation only with the thalamus and left superior frontal gyrus, whereas mPFC connectivity was restricted solely to other mPFC areas.

Developmental disruptions to the DMN may impact other emergent capacities in parallel

Many of the same brain regions (e.g., mPFC, ACC, PCC) implicated in the DMN are also thought to contribute to theory of mind, prospection and autobiographical memory, processes which, like the DMN, rely upon imagery, self-reflection and self-awareness.^{22,23} Despite a striking lack of studies examining the development of neural networks underlying these capacities (notable exception²⁴), their developmental trajectory is well described. Here, the emergence of episodic autobiographical memory for events specific in time and in place (e.g., “I remember the look of horror on my mother’s face when I ran onto the street”) is thought to occur at about 4 years of age,²⁵ around the same time that children become aware of simple causal relations among desires, emotions and outcomes in others.²⁶ The capacity for episodic memory, in particular, is thought to develop as a result of increasing self-awareness²⁷ that allows for the integration of new experiences into one’s sense of self as a continuous entity across time and prospectively into the future.^{28,29} At the same time, young children show increasing detachment from egocentric representations that allows for more sophisticated mental representations of others’ thoughts and feelings.³⁰ In subsequent years, children aged 5–10 years develop an improved awareness that memories of past events,³¹ biases and expectations³² impact other people’s emotional responses to current events and begin to hold in mind and compare multiple perspectives simultaneously.³³

Exposure to events (e.g., early-life trauma) that disrupt this developmental trajectory may have shared consequences, forestalling subsequent development across a host of systems, including the DMN, that draw upon many of the same underlying processes and neural substrates. For example, it has been shown that early-life trauma is associated with lower fractional anisotropy in the middle and posterior

corpus callosum.³⁴ Lower fractional anisotropy is thought to indicate less myelination of the fibre tract, which in the case of early-life trauma could stem from a suppression of glial cell division by stress hormones.¹⁹ In the study by Jackowski and colleagues,³⁴ fractional anisotropy scores were significantly correlated with anxiety scores. Convergent, smaller volumes of the corpus callosum have been described in both children^{35,36} and adults^{37,38} with PTSD after severe childhood maltreatment. The limited anterior-posterior integration of the DMN described in adult patients with PTSD could therefore stem from underlying processes influenced by early-life trauma like the myelination of the corpus callosum. However, in a sample of psychiatric inpatients, only half the children found to have smaller corpus callosum volumes had diagnosed PTSD,³⁹ indicating that these disruptions might not be specific to PTSD. Instead, similar disruptions could underlie different stress-related disorders previously associated both with early-life trauma⁴⁰ and alterations in the DMN (for a review see Broyd and colleagues⁴¹), such as depression. To date, the empirical evidence for DMN alterations in depression is still sparse. However, first investigations in mixed (traumatized and nontraumatized) samples of patients with depression indicate that depression is characterized by a different pattern of DMN connectivity,^{42,43} which does not mirror the developmental stages outlined above. Future studies should therefore investigate the specificity of the DMN alterations described in patients with PTSD in comparable samples of patients with childhood abuse-related depression.

Typically, adults with chronic PTSD due to early-life trauma exhibit remarkable deficiencies in functions reliant upon self-referential processing such as emotion recognition and emotional awareness.⁴⁴ Alexithymia, the inability to appropriately recognize one's own emotions, is known to be widespread in early-traumatized PTSD populations.⁴⁵⁻⁴⁸ It is also widely acknowledged that repeated exposure to traumatic events can affect one's sense of an adaptive and agentive self. This is illustrated by altered posttraumatic cognitions⁴⁹ and disrupted self-referential processing in patients with PTSD,^{50,51} arguably the most severe example being dissociative symptoms that may include depersonalization and identity disturbance (for a review see Lanius and colleagues⁵²). Neuroimaging studies suggest that dissociative experiences involve brain regions also implicated in the DMN, including the mPFC and medial parietal cortex⁵³⁻⁵⁵ and the angular gyrus.⁵⁶⁻⁵⁸ Finally, although results are conflicting, a number of studies also point toward impoverished recollection of episodic events in survivors of early-life trauma, particularly among those in whom PTSD develops as a result of this exposure (see a recent review⁵⁹).

Conclusion

The clinical importance of DMN connectivity assessed during rest in trauma-related disorders requires further elucidation. In particular, there is a critical need for studies that assess the ability of traumatized persons to flexibly transition between resting and task-oriented states.⁶⁰ Additional systematic studies that employ a lifespan developmental psy-

chopathology perspective to examine the relation between clinically noted abnormalities in self-referential processing, autobiographical memory, prospection and theory of mind in childhood maltreatment-related PTSD and the functional status of the DMN are urgently required. Moreover, the functional connectivity of the DMN remains to be investigated in children exposed to severe maltreatment. At this juncture, we can therefore only speculate that the deficiencies we previously described in adults with PTSD due to childhood maltreatment¹ stem directly from disruptions of the maturation process leading to the evolvment of the interconnected DMN and its associated psychological functions as described in healthy children older than 9 years.

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