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-analysis[7] 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 infants[3] 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 colleagues[4] 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 colleagues'[3] 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 colleagues[4] 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 colleagues[5] 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. Disruptions 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 childhood[1] closely paralleled that observed in Fair and colleagues'[2] 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 Scale[21] (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 exeption[24]), 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 casual 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-awareness[27] 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 expectations[32] 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. Convergently, 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 trauma[40] and alterations in the DMN (for a review see Broyd and colleagues[41]), 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 cognitions[49] 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 colleagues[52]). Neuroimaging studies suggest that dissociative experiences involve brain regions also implicated in the DMN, including the mPFC and medial parietal cortex[53–55] 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 review[59]).

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 psychopathology 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 maltreatment[1] stem directly from disruptions of the maturation process leading to the evolvement of the interconnected DMN and its associated psychological functions as described in healthy children older than 9 years.

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References

1. Bluhm RL, Williamson PC, Osuch EA, et al. Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. *J Psychiatry Neurosci* 2009;34:187-94.
2. Fair DA, Cohen AL, Dosenbach NU, et al. The maturing architecture of the brain's default network. *Proc Natl Acad Sci U S A* 2008;105: 4028-32.
3. Fransson P, Skiold B, Horsch S, et al. Resting-state networks in the infant brain. *Proc Natl Acad Sci U S A* 2007;104:15531-6.
4. Gao W, Zhu H, Giovanello KS, et al. Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. *Proc Natl Acad Sci U S A* 2009;106:6790-5.
5. Thomason ME, Chang CE, Glover GH, et al. Default-mode function and task-induced deactivation have overlapping brain substrates in children. *Neuroimage* 2008;41:1493-503.
6. Fransson P, Skiold B, Engstrom M, et al. Spontaneous brain activity in the newborn brain during natural sleep — an fMRI study in infants born at full term. *Pediatr Res* 2009;66:301-5.
7. Spreng RN, Mar RA, Kim AS. The common neural basis of autobiographical memory, prospection, navigation, theory of mind and the default mode: a quantitative meta-analysis. *J Cogn Neurosci* 2009;21:489-510.
8. Northoff G, Heinzel A, de Greck M, et al. Self-referential processing in our brain: a meta-analysis of imaging studies on the self. *Neuroimage* 2006;31:440-57.
9. Buckner R, Andrews-Hanna J, Schacter D. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 2008;1124:1-38.
10. Schneider F, Bermpohl F, Heinzel A, et al. The resting brain and our self: self-relatedness modulates resting state neural activity in cortical midline structures. *Neuroscience* 2008;157:120-31.
11. Northoff G, Bermpohl F. Cortical midline structures and the self. *Trends Cogn Sci* 2004;8:102-7.
12. Raichle ME, MacLeod AM, Snyder AZ, et al. A default mode of brain function. *Proc Natl Acad Sci U S A* 2001;98:676-82.
13. Gusnard DA, Akbudak E, Shulman GL, et al. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A* 2001;98:4259-64.

14. Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci* 2001;2:685-94.
15. Raichle ME, Gusnard DA. Intrinsic brain activity sets the stage for expression of motivated behavior. *J Comp Neurol* 2005;493:167-76.
16. Kim H. Dissociating the roles of the default-mode, dorsal, and ventral networks in episodic memory retrieval. *Neuroimage* 2010;50: 1648-57.
17. Sajonz B, Kahnt T, Margulies DS, et al. Delineating self-referential processing from episodic memory retrieval: common and dissociable networks. *Neuroimage* 2010;50:1606-17.
18. Uddin LQ, Clare Kelly AM, Biswal BB, et al. Functional connectivity of default mode network components: correlation, anticorrelation, and causality. *Hum Brain Mapp* 2009;30:625-37.
19. Hermoye L, Saint-Martin C, Cosnard G, et al. Pediatric diffusion tensor imaging: normal database and observation of the white matter maturation in early childhood. *Neuroimage* 2006;29:493-504.
20. Bernstein DP, Stein JA, Newcomb MD, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl* 2003;27:169-90.
21. Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician-Administered PTSD Scale. *J Trauma Stress* 1995;8:75-90.
22. Rabin JS, Gilboa A, Stuss DT, et al. Common and unique neural correlates of autobiographical memory and theory of mind. *J Cogn Neurosci* 2010;22:1095-111.
23. Spreng RN, Grady CL. Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *J Cogn Neurosci* 2010;22: 1112-23.
24. Saxe RR, Whitfield-Gabrieli S, Scholz J, et al. Brain regions for perceiving and reasoning about other people in school-aged children. *Child Dev* 2009;80:1197-209.
25. Usher JA, Neisser U. Childhood amnesia and the beginnings of memory for four early life events. *J Exp Psychol Gen* 1993;122:155-65.
26. Bartsch K, Wellman HM. *Children talk about the mind*. New York (NY): Oxford University Press; 1995.
27. Povinelli DJ, Landau KR, Perilloux HK. Self-recognition in young children using delayed versus live feedback: evidence of a developmental asynchrony. *Child Dev* 1996;67:1540-54.
28. Howe ML, Courage ML. The emergence and early development of autobiographical memory. *Psychol Rev* 1997;104:499-523.
29. Levine B. Autobiographical memory and the self in time: brain lesion effects, functional neuroanatomy, and lifespan development. *Brain Cogn* 2004;55:54-68.
30. Flavell JH. Cognitive development: children's knowledge about the mind. *Annu Rev Psychol* 1999;50:21-45.
31. Flavell JH, Miller PH. Social cognition. In: Damon W, Kuhn D, Siegler RS, editors. *Handbook of child psychology. Vol. 2. Cognition, perception and language*. 5th ed. New York (NY): Wiley; 1998. p. 851-98.
32. Pillow BH, Henrichon AJ. There's more to the picture than meets the eye: young children's difficulty understanding biased interpretation. *Child Dev* 1996;67:803-19.
33. Perner J, Wimmer H. "John *thinks* that Mary *thinks* that..." attribution of second-order beliefs by 5- to 10-year-old children. *J Exp Child Psychol* 1985;39:437-71.
34. Jackowski AP, Douglas-Palumberi H, Jackowski M, et al. Corpus callosum in maltreated children with posttraumatic stress disorder: a diffusion tensor imaging study. *Psychiatry Res* 2008;162:256-61.
35. De Bellis MD, Keshavan MS, Clark DB, et al. Developmental traumatology. Part II: brain development. *Biol Psychiatry* 1999;45:1271-84.
36. De Bellis MD, Keshavan MS, Shifflett H, et al. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. *Biol Psychiatry* 2002;52:1066-78.
37. Villarreal G, Hamilton DA, Graham DP, et al. Reduced area of the corpus callosum in posttraumatic stress disorder. *Psychiatry Res* 2004;131:227-35.
38. Kitayama N, Brummer M, Hertz L, et al. Morphologic alterations in the corpus callosum in abuse-related posttraumatic stress disorder: a preliminary study. *J Nerv Ment Dis* 2007;195:1027-9.
39. Teicher MH, Dumont NL, Ito Y, et al. Childhood neglect is associated with reduced corpus callosum area. *Biol Psychiatry* 2004;56:80-5.
40. Bremner JD. Neuroimaging in posttraumatic stress disorder and other stress-related disorders. *Neuroimaging Clin N Am* 2007;17: 523-38.
41. Broyd SJ, Demanuele C, Debener S, et al. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev* 2009;33:279-96.
42. Bluhm R, Williamson P, Lanius R, et al. Resting state default-mode network connectivity in early depression using a seed region-of-interest analysis: decreased connectivity with caudate nucleus. *Psychiatry Clin Neurosci* 2009;63:754-61.
43. Greicius MD, Flores BH, Menon V, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biol Psychiatry* 2007;62:429-37.
44. Frewen P, Lane RD, Neufeld RW, et al. Neural correlates of levels of emotional awareness during trauma script-imagery in posttraumatic stress disorder. *Psychosom Med* 2008;70:27-31.
45. Frewen PA, Dozois DJA, Neufeld RWJ, et al. Meta-analysis of alexithymia in posttraumatic stress disorder. *J Trauma Stress* 2008;21:243-6.
46. Yehuda R, Steiner A, Kahana B, et al. Alexithymia in Holocaust survivors with and without PTSD. *J Trauma Stress* 1997;10:93-100.
47. Krystal H, Krystal JH. *Integration and self-healing: affect, trauma, alexithymia*. Hillsdale (NJ): Analytic Press; 1988.
48. Badura AS. Theoretical and empirical exploration of the similarities between emotional numbing in posttraumatic stress disorder and alexithymia. *J Anxiety Disord* 2003;17:349-60.
49. Foa EB, Ehlers A, Clark DM, et al. The posttraumatic cognitions inventory (PTCI): development and validation. *Psychol Assess* 1999;11:303-14.
50. van der Kolk BA, Courtois CA. Editorial comments: complex developmental trauma. *J Trauma Stress* 2005;18:385-8.
51. Cloitre M, Scarvalone P, Difede JA. Posttraumatic stress disorder, self- and interpersonal dysfunction among sexually retraumatized women. *J Trauma Stress* 1997;10:437-52.
52. Lanius RA, Vermetten E, Loewenstein RJ, et al. Emotion modulation in PTSD: clinical and neurobiological evidence for a dissociative subtype. *Am J Psychiatry* 2010;167:640-7.
53. Lanius RA, Williamson PC, Boksman K, et al. Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. *Biol Psychiatry* 2002;52:305-11.
54. Hopper JW, Frewen PA, van der Kolk BA, et al. Neural correlates of reexperiencing, avoidance, and dissociation in PTSD: symptom dimensions and emotion dysregulation in responses to script-driven trauma imagery. *J Trauma Stress* 2007;20:713-25.
55. Simeon D, Guralnik O, Hazlett EA, et al. Feeling unreal: a PET study of depersonalization disorder. *Am J Psychiatry* 2000;157: 1782-8.
56. Blanke O, Mohr C, Michel CM, et al. Linking out-of-body experience and self processing to mental own-body imagery at the temporoparietal junction. *J Neurosci* 2005;25:550-7.
57. Bunning S, Blanke O. The out-of body experience: precipitating factors and neural correlates. *Prog Brain Res* 2005;150:331-50.
58. Arzy S, Thut G, Mohr C, et al. Neural basis of embodiment: distinct contributions of temporoparietal junction and extrastriate body area. *J Neurosci* 2006;26:8074-81.
59. Moore SA, Zoellner LA. Overgeneral autobiographical memory and traumatic events: an evaluative review. *Psychol Bull* 2007;133: 419-37.
60. Daniels J, McFarlane AC, Bluhm RL, et al. Switching between executive and default mode networks in posttraumatic stress disorder: alterations in functional connectivity. *J Psychiatry Neurosci* 2010;35:258-66.