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Wang et al. - Understanding ELS effects on default-mode connectivity - Page 1

**Toward understanding developmental disruption of
default-mode network connectivity due to early-life stress**

Commentary

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Early-life stress (ELS) constitutes a major risk factor for the development and persistence of many forms of psychopathology, leading to long-term negative consequences. In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Zeev-Wolf and colleagues (1) report on a unique cohort of children from Gaza border region in Israel, who were followed prospectively from early childhood and throughout a period in which they were exposed to war threat. The reported findings shed important new light on effects of ELS on functioning and development of the default-mode network (DMN), a constellation of brain areas that has been implicated in internally directed cognition when not engaged in goal-directed tasks, in episodic memory, and in social or self-referential information processing (2). Using magnetoencephalography, the authors find impairments in DMN connectivity in exposed preadolescents and their mothers in distinct frequency bands: alpha for mothers, and theta for children, indicating that chronic stress exposure may have distinct effects in different developmental windows. Disruptions in DMN connectivity were also associated with behavioral and hormonal parameters that were collected prospectively: in children, intrusive parenting styles of mothers as well as cortisol levels independently predicted impaired DMN connectivity. In mothers, cortisol levels measured in their children, as well as self-reported emotional distress in the mothers themselves, predicted later disruptions in DMN connectivity.

Previous work on long-term sequelae of ELS has relied on a variety of self-report instruments to retrospectively assess exposure to childhood maltreatment, such as Childhood Trauma Questionnaire (CTQ), Care and Abuse questionnaire (CECA-Q), Adverse Childhood Experience (ACE), and Conflict Tactics Scale (CTS). Among these, there is a large variety in multiplicity and severity of childhood trauma exposure. There is furthermore an extensive literature on disparate effects of various types of ELS, and ELS experienced at different developmental stages, on adult brain structure, cognitive function, and behavior (3). The current paper makes an important contribution in disentangling a number of potential confounding factors. First, one weakness of many previous studies is that ELS effects may be explained by other factors that are associated with ELS, such as malnutrition, poverty, or lack of medical care. Zeev-Wolf et al.'s cohort from Israel excludes these potential confounds, not only because the type of ELS in

this sample is highly homogeneous, but also because exposure to war threat occurred in an otherwise functioning society. Second, retrospective reports of ELS may be colored by an individual's current emotional state or context, especially when retrieving memories from very early childhood, casting doubt on the veracity of such self-report measures and introducing another potential confound. The current study circumvents this issue by investigating both children and mothers prospectively at multiple time points starting already in early childhood (reported data was acquired at mean ages of 2.8 years, 9.3 years, and 11.8 years). Third, social support from close relatives during ELS exposure may constitute a critical resilience factor. Zeev-Wolf et al. addressed this issue through observation of dyadic interactions between mother and child at different ages. While intrusive parenting styles are also reported to be associated with disruptions in later DMN connectivity, this association was found across both exposed and control groups, suggesting that both factors, threat exposure and intrusive parenting, may independently exert a similar long-term effect on brain development.

The current findings in both children and mothers are an important contribution to a growing literature pointing toward an effect of ELS in impairing DMN connectivity. For instance, earlier studies demonstrated that healthy individuals who report a history of ELS have reduced connectivity within DMN, measured using resting-state functional MRI. Another study showed that posterior cingulate cortex/precuneus seed-based DMN connectivity is decreased in post-traumatic stress disorder (PTSD) patients with a history of ELS, and resting-state connectivity between the DMN and the amygdala was shown to predict PTSD symptoms arising from ELS (3). However, DMN dysfunctions are not specific to ELS. For instance, Sripada et al. showed that long-term poverty can cause reduced DMN connectivity (4), and DMN impairment has more broadly been associated with PTSD symptoms as well as other forms of psychopathology (2). In contrast to these relatively consistent findings regarding DMN, a review of other ELS effects on brain structure and function concluded that many of these, including grey-matter volume, cortical thickness, and fiber-tract integrity, are specific to distinct types of childhood maltreatment (e.g., parental verbal abuse, domestic violence, childhood sexual abuse, etc.) (3). Thus, while more research is needed to provide insight into stressor-specific effects on brain structure and function,

reduced DMN functioning appears to be the most consistently reported aberration across many different forms of ELS, or even chronic stress in any life period.

Developmental work has shown that the maturation of the DMN involves a gradual process of integration of distributed brain regions. Within the first year of development, individual nodes of the DMN can already be identified using independent component analysis, but the characteristic connectivity between anterior (e.g., medial prefrontal cortex) and posterior (e.g., posterior cingulate cortex) parts of the DMN is not yet seen. This anterior-posterior integration only reaches a level comparable to adults by approximately nine years of age. Thus, early childhood may constitute a critical time window during which exposure to trauma can disrupt the development of the DMN (5). In line with the current paper's finding that cortisol levels predict DMN connectivity, this disruption may be partly explained by structural changes caused by increased stress-hormone exposure. For instance, stress hormones are thought to hamper myelination of white matter tracts critical for long-range anterior-posterior network communication (5), and to decrease volume as well as synaptic density of the hippocampus (3), a region within the DMN.

Exposure to stress hormones, however, is also known to have acute consequences for functioning of large-scale networks. Such networks often activate reciprocally, and stress hormones are known to play an important role in regulating the balance in resource allocation between these networks. For instance, Hermans et al. (6) argued that excessive catecholamine release in response to acute stress impairs prefrontal cortex, and therefore core regions of both the DMN and the executive control network (ECN). By contrast, stress-levels of catecholaminergic activity are thought to increase neuronal excitability in the amygdala, a core region of the salience network (SN). Together, acute stress thereby appears to shift the balance between these networks away from ECN and DMN, and toward SN. Rapid, non-genomic effects of glucocorticoids may also play a key role in fine-tuning the acute response to stress, for instance by releasing GABAergic control of the amygdala, a mechanism that involves the endocannabinoid system (7). The balance between glutamatergic and GABAergic neurotransmission within the posterior cingulate cortex, a node within the DMN, has furthermore shown to be correlated with

connectivity within the DMN (8). Slow, gene transcription-dependent effects of glucocorticoids have finally been implicated in the return to homeostasis, and a rebalancing of large-scale networks, in the aftermath of acute stress (6). Long-term effects of ELS on large-scale network function may therefore also result from alterations in functioning of stress-sensitive neuroendocrine systems.

Controlled experimental manipulation of ELS in rodents has yielded important insight into how different forms of ELS result in lasting changes in such stress-hormone systems. While milder forms of ELS trigger *hyperresponsiveness* of the HPA axis, more severe ELS results in *hypocortisolism* (9), and manipulations of glucocorticoid effects in adulthood may also alleviate symptoms caused by ELS. Hypocortisolism is also observed in PTSD, but particularly in patients with a history of ELS, and is thought to stem from enhanced HPA-axis negative feedback. Core regions of the DMN, medial prefrontal cortex and hippocampus, are critically involved in the negative feedback loop of the HPA axis. Recently, Atsak et al. found that ELS can also cause persistent disturbances in the endocannabinoid system (10), which interfere with the pathways by which glucocorticoids regulate stress adaptation and which may hamper regulation of the balance between inhibitory and excitatory neurotransmission. Thus, these findings provide initial insight into how ELS-related dysfunctions at the level of large-scale networks such as DMN may result not only from structural changes, but also from chronic dysregulations in stress-regulatory hormonal systems. More research will be needed to establish if the effects of ELS on DMN function, as observed in the current study and earlier work, may be reversible through interventions targeted at normalizing functioning of these systems.

In conclusion, ELS can alter the developmental course of neuroendocrine function as well as of brain structure and function up to the level of coordination of large-scale brain networks. Prospective studies such as the one performed by Zeev-Wolf et al. (1) are essential for disentangling the effects of different types of ELS, at different developmental stages of exposure. Such prospective efforts, preferably also including prospective measures of brain structure and function, will need to be complemented by experimental work in rodents, in which more invasive techniques can be used to study the underlying neurobiological mechanisms.

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Disclosures

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