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Review

Fetal Programming of Brain and Behavior through Ionizing Radiation

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Abstract: For decades, the Barker hypothesis and thrifty phenotype hypothesis have driven researchers to explore the development of metabolic syndrome through fetal programming. In this short review, we provide peer-reviewed support for the fetal programming of neural genetic activity and behavior in multiple neural regions: the prefrontal cortex, the cerebral cortex, the hippocampus, the cerebellum, and the hypothalamic–pituitary–adrenal axis. We also introduce ionizing radiation as a purported indirect driver of phenotypical changes. The predisposition of brain and behavioral phenotypes after gestational exposure to stressors can lead to aversive and harmful outcomes, rather than protective adaptations.

Keywords: fetal programming; ionizing radiation; stress; behavior; hypothalamic-pituitary-adrenal axis

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1. Introduction: Brain and Behavior

Behavior is simply defined as an organism's activity that can be observed or measured [1]. Behaviors are internally coordinated and are produced in response to internal and external stimuli. Sexual reproduction, resource gathering, predation, and survival rely on appropriate behavioral responses to stimuli and those responses have the ability to change within individuals of most species [2–5]. Modifications in normative behavior can occur during an organism's lifespan through experiential learning. Organisms learn to avoid or carefully approach high-risk situations through first-hand or observational experiences [6,7]. In contrast, rewards lead to an increased likelihood of repetitive behavioral responses [8]. This is an operant conditioning paradigm of learning; classical conditioning may also modify behavior through association and reinforcement [1]. Phenotypical behavior changes may occur through epigenetic mechanisms, serving as evolutionary adaptation and plasticity to enhance survival and fitness; however, they may also predispose an organism towards maladaptive impulses and pathophysiology [9].

Changes in behavior may lead to increased chances of survival and enhanced fitness; however, not all modifications lead to a positive result for the individual. Modifications may lead to the progression of disease or disorders and are considered maladaptive [10,11]. Reward-seeking behavior influencing addictions can develop from short-term reward-based and disrupted learning processes [10,12]. The ability to inhibit responses and focus on long-term rewards instead of short-term rewards is less likely to influence addictions [13]. Inhibition and impulsivity have been linked to poor academic performance and risk-taking behaviors, such as gambling [14,15]. Obsessive compulsive disorder, post-traumatic stress disorder, major depressive disorder, and schizophrenia are all psychological disorders with significant maladaptive behaviors that disrupt the ability for individuals to function properly [16,17]. These disorders not only highlight maladaptive behavior but also neurological dysfunction in various regions and organizational levels [18].

The brain is comprised of specialized electrochemical cells called neurons that influence behavior and cognition. Neurons were first introduced to the world in detail in the

1800s by Camillo Golgi and Santiago Ramón y Cajal, who was also the founder of the concept of plasticity [19,20]. Plasticity refers to environmentally dependent phenotype expression (an organism's ability to adapt and change to its environment [21]). Neurons are physiologically diverse and function in circuits that are separated regionally. During fetal development and for a period after birth, mammalian neural circuitry undergoes significant modifications to structure and connectivity [22]. This period of development is sensitive to environmental factors and may lead to neurological and behavioral disorders later in life if exposed to stressful and inadequate conditions [23,24]. Most mammals have functional homology, making comparative biology a reasonable experimental process for understanding both human and animal behavior and disease.

2. Fetal Programming of Brain and Behavior

Fetal programming explains the process whereby early environments influence the physiological phenotype of the offspring [25,26]. Sometimes referred to as the Barker hypothesis and originally referred to as the thrifty phenotype hypothesis, Hales and Barker described the phenomenon in 1992 [27]. The researchers associated early-life nutritional deprivation with the development of adult metabolic syndrome. Through replication and further study, developmental plasticity during the fetal period of gestation became the forefront of consideration of evolutionary processes, hypothesizing that the adaptation to deficient environments would lead to development of the disease [28,29].

Over the progress of fetal programming research, it became clear that nutritional deprivation was not the only prenatal stressor that could lead to maladaptive phenotypes. Malnutrition has been hypothesized to influence programming through several mechanisms, such as inflammation, oxidative stress, dysregulated metabolism, a decrease in placental enzymes, and an increase in steroidal hormones [30,31]. Maternal plasma glucocorticoid levels have been shown to be increased with food restriction, along with the activation of the hypothalamic–pituitary–adrenal axis and a decrease in glucocorticoid-binding factors, leading to higher concentrations of active hormones free to interact with the fetus [32,33]. Through the administration of exogenous steroids, glucocorticoids could stimulate the same physiological phenotype as malnutrition, which displays hypertension, hyperglycemia, hyperinsulinemia, and changes in behavior [34]. Active endogenous glucocorticoids are prevented from interacting with the fetus via an enzymatic barrier present in the placenta, the 11β-hydroxysteroid dehydrogenase type 2 (11β2HSD), which catalyzes the conversion of cortisol into cortisone. If the endogenous hormone concentrations are high, or if the mother is exposed to synthetic hormones, which are poor substrates, the enzymatic barrier is inefficient, and glucocorticoids will interact with the fetus [34]. Exogenous hormones are often given for organ maturation for mothers at risk of preterm labour and lead to alterations in behavior, including hyperactivity, reduced cognitive function, and anxiety-related behavior in the offspring [35–37]. Endogenous hormones circulating due to maternal stress, such as anxiety, have also been linked to increased anxiety in their children [38]. Once glucocorticoids bind to their receptors, they are able to change gene expression directly, by enabling DNA methylation and by the production of reactive oxygen species (ROS) [39,40].

3. Ionizing Radiation as a Stressor

Stress is defined as an internal or external stimulus with a perceived threat to our survival and health [41]. Stress may be an illness, injury, familial loss, mental-health issue, or exposure to xenobiotics (Figure 1). Once exposed to a stressor, the body may react via the production of glucocorticoids, which may produce ROS [39,40,42]. ROS may also be produced through direct and indirect mechanisms of ionizing radiation. Ionizing radiation is the emission or transmission of energy, either through a particle or a wave, that has sufficient energy to remove an electron from an atom or molecule, producing a highly reactive ion or free radical [43]. Free radicals, also known as ROS, can induce direct DNA damage and cellular oxidative stress [44].

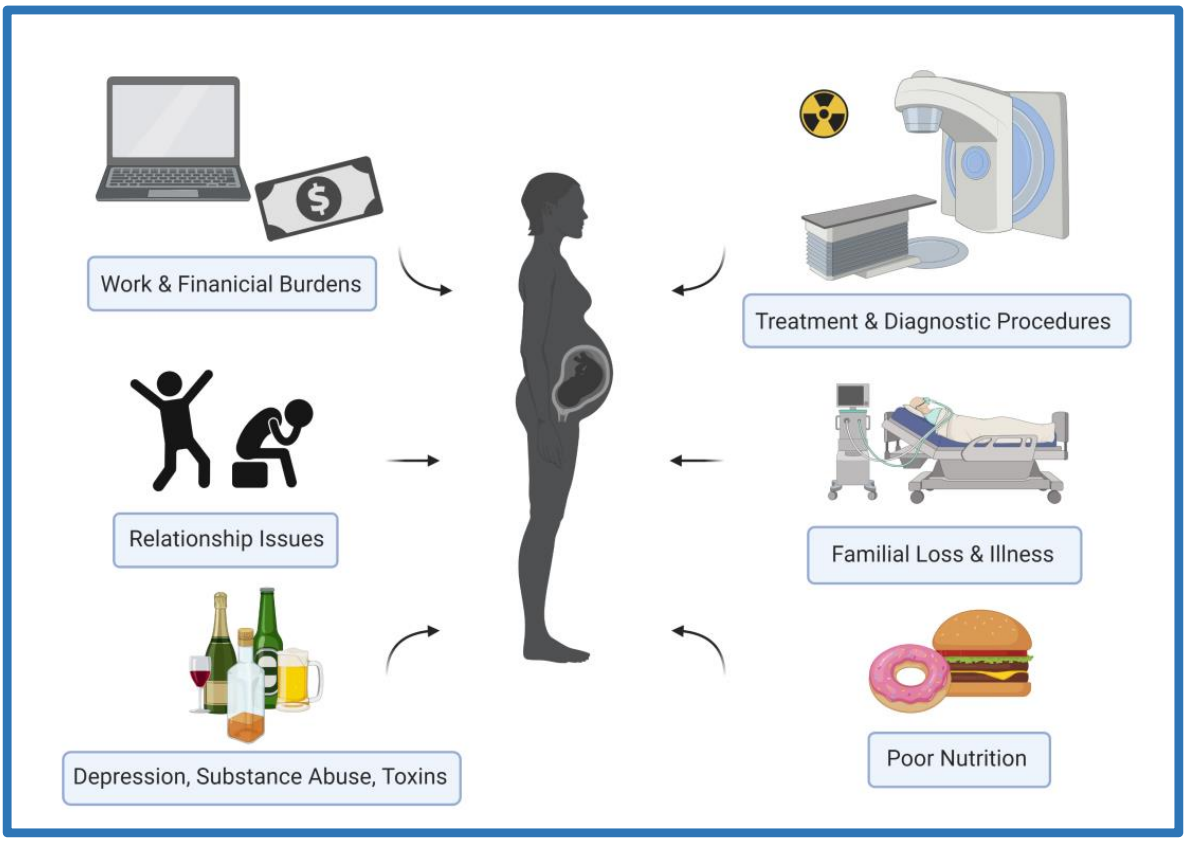

Figure 1. Various maternal stressors. Created with BioRender.com.

Prenatal exposures to ionizing radiation may come from diagnostic imaging or workplace exposures [45]. Primarily, diagnostic imaging through X-rays and computed tomography (CT) scans are low linear energy transfer (LET) radiation exposures. DNA damage through low LET exposure is predominantly through indirect chemical processes from radiolysis reactions, where energized particles interact with water molecules within the cell, transferring energy, thereby ionizing the molecule and creating ROS [46]. The extent of the damage incurred from these processes is related to individual, genetic susceptibility with DNA repair systems, the dosage, and the stage of development if a fetus or infant is exposed, leading to chromatid and chromosomal aberrations and instability that may be transmissible to future generations through fetal programming and epigenetic mechanisms [47]. In early gestation, exposure to radiation can lead to fatality and significant organogenesis disruption. Malformities in appendages, growth restriction, and neuronal death in rodents are a few of the postnatal effects listed in a review conducted by Sreetharan and colleagues [45]. Exposures of 100–3000 mGy in late gestation led to neuronal cell loss, decreases in overall neural volume, and behavioral [48] changes [45]. However, diagnostic exposures are considered low-dose ionizing radiation, which has been shown to have a horemetic response, whereby doses may provide protection, rather than significant damage that increases linearly [49–52]. Single and multiple exposures of CT scans to cancer-prone TRP58 heterozygous mice have been shown to extend lifespan due to an increased latency to develop cancer and a slowed progression of existing tumors, respectively [51,52]. Dose rate, as a variable, should also be carefully considered, as research provides evidence of significant physiological and morphological outcomes at low dose rates. Low dose rates of 0.2 and 0.4 mGy/hr during zebrafish neurological development produced numerous deleterious outcomes, including an increase in mortality, malformities, and physical malfunction [48]. Evaluation of timing, dosage, dose rates, and the heritable effects is important in understanding safety and adverse phenotypes; here, we focus on dosage during late gestation.

3.1. The Prefrontal and Cerebral Cortices

The prefrontal cortex (PFC) is new on the scale of neurological evolution and is responsible for complex behavior and cognition; however, it is not specifically defined based on structure or function [53]. Research links the region to emotion, social interaction, and decision making—all components of cognition [54]. Reflexive behaviors are stereotyped and the focal point of other neural structures, but the PFC is known for top-down processing, whereby behavior may be influenced by stimuli input, providing contextually relevant responses.

In order for the PFC to produce contextually appropriate responses, it requires environmental feedback from other neural regions. A key pathway connects the PFC to the basolateral amygdala (BLA), a structure that regulates emotion. The BLA provides significant positive feedback in early development that gradually declines with maturity; however, this decline is accelerated under stress, such as maternal deprivation [55,56]. Disruption of BLA input, through optogenetic manipulation, induces synaptic depletion and interferes with fear-cue learning processes [57]. Chronic stress to rodents, such as random exposure to restraint, forced swim in cool water, tilted cages, and shaking cages for fourteen days, leads to a decline in inhibition feedback, inducing abnormal aggression, inability to recognize novel objects, and increased locomotive activity [58]. Reversal of all abnormal behaviors was possible with the introduction of a designer receptor exclusively activated by designer drugs (DREADDs) to reactivate connectivity between the PFC and the BLA. Fetal programming through irradiation is supported by previous research involving various radiation sources, multiple doses, and different gestational timings. Low-dose exposures of 100 mGy–1000 mGy to C57Bl/6J radioresistant mice during gestational day (GD) 11 produced a dose response in physical and social behaviors as well as in anxiety and cognitive measures in conditions as low as 100 mGy [22,59–61]. Correlated with these responses, changes in frontal cortex volume and cerebella volume were noted with a 31% and 33% decrease, respectively [62,63].

The cerebral cortex in primates is convoluted to increase surface area; in rodents, it is smooth, but it is still located on the surface and is divided into functional regions called lobes. Often, the cerebral cortex and the prefrontal cortex are used interchangeably in the literature and may seem ambiguous; however, the neural function of the PFC is distinct [64–66]. Here, we focus on the cortical region involved in stimuli processing. Research into this region has correlated impoverished environments that are reduced in sensory and motor stimulation with a decline in stimuli processing development [67]. To explore the modification of the cerebral cortex's visual processing, pre-weaned rat pups and their mothers were placed in opaque cages to limit visual input. The effects of rearing pups in a diminished environment led to a delay in weight gain, visual maturity, motor activity, and a reduction in the brain-derived neurotropic factor (BDNF), insulin-growth factor-1 (IGF-1), and glutamate decarboxylase (GAD) gene expression. Prenatally malnourished rats show diminished β-adrenoceptor and BDNF expression levels, as well as impaired learning through long-term-potentiation deficiencies and visuospatial issues [68]. Expression levels and other functions were restored with exposures to environmental enrichment, lending to the concept of adaptive modifications and plasticity in brain function. Late gestational exposure to synthetic glucocorticoids increased the regulation of early growth response 1 (EGR1) in the cerebral cortices and hippocampi of guineapigs [69,70]. EGR1 expression is linked to neuronal activation and is indicative of physiological changes in the cerebral cortices.

Earlier research exposing 1000 mGy of ionizing radiation on either GD 13, 15, or 17 to rats led to thinning of the cortices and differential physical development and function [71]. On GD 15, pregnant Sprague-Dawley rats were exposed to whole-body X-rays of 0, 25, 50, 75, or 125 R, which demonstrated significant morphological changes to the frontal and cerebral cortices [72]. The resulting changes were dose-dependent, were matched by changes in body weight, and were more striking with age. A decrease in cortical thickness was measured and noted to be 1/2 the thickness of age-matched controls, with a loss of neurons

as the contributing factor. Using a larger mammalian model, 13 macaques were irradiated with 175–600 cGy in either early or mid-gestation and were raised along with 7 controls, resulting in a significant reduction in frontal cortex volume by 26 and 29%, respectively [73]. Notably, ionizing radiation exposures to the prefrontal cortex during the first trimester in humans may be linked to neurological disorders, such as schizophrenia [74,75]. Within the cerebral cortex, however, X-ray exposure delays neuronal migration in infant brains and gamma irradiation has led to neuronal loss and defects [76,77]. The ambiguity and interchangeability of the terms prefrontal cortex and cerebral cortex throughout the literature add a level of uncertainty to distinct regional changes with respect to fetal programming. A clear separation of anatomical regions is required to provide a clear representation of genetic phenotypes.

Another brain region providing feedback to the PFC is the hippocampus, a structure foremost known for learning and memory, which is also connected to the amygdala. The connection between the PFC and the hippocampus provides experiential context based on episodic memory formation and retrieval [62]. Multiple early-life insults, from nutritional deficiencies to smoking and alcohol exposures, have been associated with cognitive disorders and memory impairments in the hippocampus and PFC [63]. Without normal development and connectivity from the PFC to these regions, behavioral responses are modified and aversive.

3.2. The Hippocampus

As previously mentioned, the hippocampus is well known for learning and memory function, which are key to appropriate behavioral responses [78,79]. The hippocampus is dense with glucocorticoid receptors and is the site of neurogenesis, which is linked to cognitive flexibility and the inhibition of depression and anxiety [80]. Multiple connections with other brain regions support the memory and learning function of the hippocampus, particularly fear cues and inhibition with feedback to the amygdala and prefrontal cortex [81]. Maternal stress has been linked to a decline in neurogenesis, correlated to decreased neuronal functionality, language delays, and decreased cognition [31]. Female rats born to dams who were restrained in late gestation had decreased levels of glucocorticoid receptors and impaired spatial learning and memory, implicating a significant disruption of hippocampal physiology and function due to prenatal stress [82]. Multiple generations of female offspring exposed to glucocorticoids have been shown to have dysregulated gene expression and DNA methylation within the hippocampus [83]. Sexual dimorphism in brain regions is not uncommon; 21-day-old Long-Evans female rats have been noted to have significant gene dysregulation related to growth factors in the hippocampus after exposure to prenatal stress [84]. Pregnant rats were stressed by placing their cages on an elevated platform for a total of 20 min per day during gestational days 12–16 and this environment was sufficiently stressful to show substantial gene regulation changes via microarray analysis, with 200 dysregulated genes in the female hippocampus compared to 167 in the males. Rat pups are not born fully developed and maternal care during early life has also been implicated in hippocampal plasticity, gene methylation, and gene expression in offspring aged 7–17 weeks [85–90].

Whole-body X-ray irradiation exposure to doses ranging between 0 and 1000 mGy to C57Bl/6J mice during early neurogenesis on gestational days 11 and 12 has shown locomotor and spatial memory deficits in the offspring [91]. In addition, forty-one genes were differentially expressed related to p53 signaling, DNA damage, apoptosis, and signal transduction, and there was a significant reduction in cortical thickness and hippocampus proliferation. X-ray exposure to C57Bl/6J mice on gestational day 11 altered post-synaptic density protein 95 (PSD95) in the hippocampi, with 1000 mGy, supporting research implicating the sensitivity of the hippocampus with stress and modifications [92]. Within the hippocampus, frontal cortex, and cerebellum changes in microRNA, methyltransferase DNMT3a, and global methyltransferase expressions were differentiated based on region and sex [93].

A decrease in volume of the hippocampus and the subsequent dilatation of the lateral ventricles were also related to prenatal X-ray exposures [94]. Swiss albino mice were exposed to 500 mGy of γ radiation between gestational days 11 and 19 and offspring were tested for a variety of behavioral responses, where exposures to all gestational-day treatment groups produced activity, anxiety, and memory deficiencies in the 3-month-old offspring [95]. Earlier exposures to pregnant C57Bl/6J mice on GD 5 to 20 cGy displayed memory and motor deficits that were sexually dimorphic [96]. Offspring were tested at three different stages of adulthood for behavioral effects and the males had pronounced changes in anxiety and learning tasks at 3 months of age that matched Cornu Ammonis fields, CA1 and CA3 pyramidal neuron counts. At 6 months, the males displayed a recovery of this behavior, which declined again at the age of 12 months. With each study, it is clear that hippocampal exposure during fetal neuronal development may produce aversive behavioral events and significant physiological modifications.

3.3. The Cerebellum

The cerebellum was originally thought to only control motor function; however, it has recently been shown to be involved in cognition, addictions, and depression [97]. Exposure to prenatal stress, such as a diet insufficient in zinc and fatty acids, leads to decreased cerebellar volume, linked to attention deficiencies, poor impulse control, and behavioral disorders [63]. C57Bl/6J offspring, prenatally exposed to high levels of folic acid, displayed significant gene dysregulation in the cerebellum in both male and females [98]. Genes differentially expressed were linked to autism disorder and neurodevelopment. In contrast to the high levels of folic acid, a study with vitamin deficiencies showed proteomic, cellular, molecular, and behavioral support of cerebellar disruption due to early-life stress [99]. In humans, a significant reduction in grey matter within multiple brain regions, notably the prefrontal cortex, cerebral cortex, and cerebellum, was associated with mid-gestation self-reported anxiety [100,101]. Cerebellar weight and volume in rat offspring were also sensitive to a single exposure to a synthetic glucocorticoid, betamethasone, in late gestation [102]. The single exposure was also associated with anxiety-related behavior and increased expression of calbindin-D28K, a neuroprotective protein whose expression is associated with levels of glucocorticoids. On GD 21, pregnant Wistar rats were X-irradiated with 2 and 2.5 Gy or exposed to a cyclotron with 0.75 and 1.5 Gy exposures [103]. Within the X-irradiated cerebella of the offspring, Purkinje cells were shorter, with irregularly oriented dendritic branches, and some failed to migrate altogether. Similar to the previously highlighted neural regions, the cerebellum is clearly sensitive to early-life stressors.

3.4. The Hypothalamic–Pituitary–Adrenal Axis

The hypothalamic–pituitary–adrenal (HPA) axis is pivotal in allostasis—adapting to stressors in order to maintain homeostasis—by utilizing glucocorticoids, hormones produced in the adrenal cortex, as a biofeedback system [104]. It is a fundamental process in driving adaptive or maladaptive responses from an organism and disruption has been associated with mental and neurological disorders, such as schizophrenia, depression, addiction, and mood disorders [104,105]. Just as with the other neural regions, the HPA axis is sensitive to early-life stress, where deprivation can lead to modifications in behavioral phenotypes [106]. For example, nine-day-old Wistar rat pups deprived of maternal care have showed increases in serotonergic activity and anxiety, indicating changes in the hypothalamus [106]. Significant research efforts have expanded the understanding of methylation and fetal programming, focusing on the HPA axis and hippocampus, due to the high density of glucocorticoid receptors and glucocorticoid feedback in these regions [70,107,108]. Furthermore, synthetic glucocorticoid administration has been associated with HPA modification, hyperactivity, and metabolic impairments [38,109].

During neuronal growth, differentiation, and migration, fetuses undergo a critical period of species-dependent development. Gestational day (GD) 11 through 17 for mice and the second trimester in humans have produced deleterious effects after environmental

exposures, such as cognitive impairments, that are both physiological and behavioral, including schizophrenia [22,110]. An early study, in 1996, exposed Sprague-Dawley rats on GD 16–18 to 4 Gy γ ionizing radiation [111]. This exposure led to the induction of neuronal stem cell death and disrupted activity levels of the p53-mediated apoptotic pathway. At a far lower dose of 15 mGy X-irradiation, another study reported physiological and behavioral changes in Wistar rat offspring exposed on GD 8 and 15 [112]. The authors noted a paucity of peer-review published effects at low doses less than 100 mGy, while their exposure produced profound adverse phenotypes. The various behavioral and genetic changes across the literature support the idea that ionizing radiation may induce behavioral adaptations in response to maternal stress. Adaptations, due to the physiological and functional changes in the brain regions presented here, may not be preferential in particular circumstances and require further study.

Neural regions interact with each other to provide feedback, control, and modulation. The hippocampus and prefrontal cortex have both been implicated in HPA modulation [113,114]. Glucose metabolism research shows prefrontal cortex activation during stressful events that is inversely related to salivary cortisol levels [114]. Hyperactivity of the HPA axis also leads to decreased prefrontal cortex activity and depressive behaviors [115]. Through lesioning, the hippocampus has been implicated as an HPA modulator due to functional changes when compared to lesions in other regions [113]. The cerebellum has reciprocal pathways connected to the hypothalamus and has been implicated in depressive symptoms, implicating HPA involvement as well [116]. The strength in the relationships between these regions and the HPA axis may implicate a strong response to prenatal stress. Unfortunately, there is a paucity of literature on the involvement of the cerebral cortex, which may be due to the ambiguity of anatomical delineation with the prefrontal cortex.

4. Conclusions

Early gestational exposures to ionizing radiation show clear and significant damage to multiple organs and molecular processes; however, late gestational changes are varied and behavioral phenotypes are not always present or investigated, which may be due to the choice of testing paradigms [117]. The neural regions previously discussed have clear sensitivities to exposures to early-life stress, such as ionizing radiation and, together, are implicated in important behavioral responses. Considering the regional influences on behavior, inhibition, sensory input, cognition, fear, and memory consolidation, this review focused on providing a portrait of behavioral and neural genetic phenotypes with respect to early-life exposures to low doses of ionizing radiation. Inhibition of risk-taking behavior and stress-coping strategies are valuable to survival and different stressors may bring about adaptive phenotypes affecting similar behavioral and genetic expression patterns.

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