# Pathways Associating Childhood Trauma to the Neurobiology of Schizophrenia

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*Abstract-* **While researchers have for decades considered the role of social factors, endocrinology, neural function, hippocampal integrity, and cognition in the development of schizophrenia, there has been a relative paucity of studies considering the participation of the stress cascade in the interplay of these elements. As described in this review, stressful exposures and stress sensitivity may plausibly be argued to play a role in the etiology, neurobiology, and course of schizophrenia and related psychotic disorders. Notably, research conducted over the last decade has made it increasingly clear that childhood traumatic experiences represent a prominent risk factor for the development of psychotic disorders, including schizophrenia. Accumulating evidence suggests that this relationship is mediated by the development of a neuropathological stress response, involving HPA axis dysregulation, aberrant functioning of different neurotransmitter systems, hippocampal damage, and memory deficits. However, it remains difficult to identify exact causal pathways linking early trauma to schizophrenia, including to the individual symptoms associated with the disorder. In addition to the strong association among early trauma, stress sensitization, and positive symptoms in schizophrenia, there is also evidence indicating that the negative and cognitive symptoms are related to these factors. However, the emergence of these symptoms may lie on a distinct and non-interacting pathway in relation to the development of the positive symptoms. The natural increases in stress sensitivity and HPA axis activity during adolescence may act on already maladaptive stress circuitry resulting from early trauma and/or a genetic predisposition to produce full blown stress sensitization and cause epigenetic effects, such as the altered methylation of different genes, that lead to schizophrenia or other psychiatric illnesses.**

***Keywords- Schizophrenia; Childhood Traumatic Experiences; Childhood Trauma; Early Trauma; Stress Sensitization; Stress Sensitivity; Neurobiology of Schizophrenia; Etiology of Schizophrenia; Epidemiology of Schizophrenia***

## I. INTRODUCTION

While an intact stress response system is essential for development and adaptation, excessive stress can be detrimental to health, behavior, and neural integrity [1, 2]. There are well-described associations among stress exposures, glucocorticoid levels (stress hormones), hippocampal integrity, and memory in humans [3-6] and in animal studies [7, 8], supporting the interrelationships of these elements in causal and reverberating pathways. Notably, early stress in animals [7, 9-13] and childhood traumatic experiences in humans [3, 14-18] are consistently linked to long-lasting and maladaptive alterations to all of these components. Pathogenic stress reactions may arise during critical developmental periods, like childhood and adolescence, following threatening exposures that are outside of everyday human experiences. In addition, genetic vulnerability, prior stress exposure, and even intergenerational stressors can influence stress sensitivity by modulating the integrity of the homeostatic elements in the stress cascade [19-21].

The convergence of knowledge about stress and its consequences drawn from widely varied models and diverse approaches is impressive. There is a clear consensus that early childhood trauma and other stressors are associated with Post Traumatic Stress Disorders (PTSD) and major depression, and even with physical health, but the association of such stressful exposures with the risk for schizophrenia is far less appreciated although every bit as compelling. This paper broadly, though not comprehensively, reviews some of the evidence for this association, including epidemiological and clinical findings, neuroanatomy, and some key molecular and cellular pathways. Included in this review is an examination of the potential causal pathways linking early trauma to the symptomatology of schizophrenia, including the positive and negative symptoms, as well as the cognitive impairments.

### *A. Schizophrenia and Early Trauma*

High rates of childhood trauma are found in psychotic samples [22-28]. For example, a recent meta-analysis [28] found that childhood adversity/trauma had an estimated population attributable-risk for psychosis of 33%. This relationship remained significant even in reviewed studies that controlled for potentially confounding variables, including genetic liability, comorbid psychopathology, drugs and cannabis use, ethnicity, educational attainment, ethnicity, urbanicity, and IQ. Furthermore, high levels of early traumatic experiences are demonstrated in patients with first-episode schizophrenia [27]. In another study [23],

researchers reported that when comparing patients with a psychotic disorder (non-affective type), their siblings, and healthy controls, childhood trauma was associated with later psychotic severity in a dose-response fashion. While the siblings reported some childhood trauma patients had significantly more exposure to early traumatic events. Given that siblings share 50% of their genes, these results suggest that environmental exposures, like childhood trauma, may account for the fact that the patients developed a psychotic disorder and their siblings did not.

Increased stress sensitivity and reactivity are often found in individuals with psychotic disorders [21, 29, 30]. In one study [29], researchers studied subjects in their natural daily environments and found that increases in perceived stress in response to various daily events and activities were related to significantly greater decreases in positive affect and increases in negative affect in both patients with a psychotic illness (that were in remission at the time of the study) and their first-degree relatives (in comparison with controls), with the patients reporting more negative affect than their relatives, even when actual stressors did not vary. These results suggest that stress sensitivity and reactivity are increased in individuals with a genetic predisposition to psychosis. Individuals with stress sensitivity will exhibit much greater distress reactions in response to traumatic events and other stressors in childhood than other individuals exposed to similar traumas. It may be the case that these early traumatic or stressful experiences, especially if recurrent, further amplify stress sensitivity to produce the full stress sensitization syndrome. Thus, it seems likely that both genetic and environmental mechanisms are at play, in which trauma may alter gene expression through epigenetic pathways, which in turn modify stress sensitivity.

Several studies indicate that acute onset of schizophrenia can follow directly upon stressful life events [31, 32], with more severe symptoms accompanying greater amounts of recent life stress [32]. For example, a meta-analysis [32] concluded that in 43% of 7 independent samples, patients with schizophrenia had significantly greater recent life stressors than healthy controls. In 86% of 16 independent samples to investigate similar measures, a significant association between elevated levels of antecedent stress and greater symptom severity was reported [32]. Rabkin [33] suggests that while such events are neither sufficient nor necessary to induce the disorder, they may precipitate its onset by exacerbating already elevated stress levels.

Prenatal stress is a risk factor for developing schizophrenia [34-36] and other psychiatric illnesses, like bipolar disorder [37]. Other prenatal (and perinatal) complications that are also risk factors for schizophrenia furthermore entail changes in glucocorticoids, including hypoxia [38], viral infections [38-40], and nutritional deficiencies [41]. In animals, prenatal nutritional deficiencies are associated with hippocampal abnormalities [42, 43]; prenatal hypoxia significantly increases plasma cortisol and ACTH levels [44] and hippocampal abnormalities [45]; and perinatal viral infections are associated with impaired hippocampal neurogenesis [46]. These results are not inconsistent with the view that numerous prenatal and perinatal complications may elevate the risk for schizophrenia through stress pathways.

### *B. Stress Related Pathology in Animal and Human Studies*

Infant animals separated from their mothers for long periods of time exhibit long-term alterations in the stress response and hypothalamic-pituitary-adrenal (HPA) axis. These changes include stress sensitivity, elevated glucocorticoid levels [7, 9-11], and increased corticotropin-releasing hormone (CRH) activity reflected by mRNA levels [7, 9]. Protracted maternal separation conditions in animals are a model for maternal deprivation or environmentally challenging conditions in humans. The consequences of these exposures include fewer glucocorticoid receptor (GR) densities/levels in the hippocampus [7, 12], such that negative feedback from the hippocampus to the HPA axis is diminished. This results in stress sensitivity, which involves an HPA axis that is over-active and excessively reactive to subsequent environmental stressors, and which further augments glucocorticoid levels and promotes hippocampal neurotoxicity. Early deprivation can thus lead to long-lasting learning and memory deficits [7, 13] and behavioral changes [7, 10, 11]. The normal age-related increases in glucocorticoid levels, hippocampal based memory and learning deficits that occur in rats [47, 48] manifest at younger ages with maternal deprivation exposure. These results support the "glucocorticoid cascade hypothesis" [5], which, in summary, posits that an overproduction of glucocorticoids causes neuronal death and atrophy in the hippocampus, which in turn disrupts hippocampal-based learning and memory and accelerates brain aging. Similarly, in humans, childhood trauma is consistently associated with reduced hippocampal volumes in adults and with dysregulation of the HPA axis in all age groups [3]. Another well-replicated finding is the association between high cortisol levels and reduced hippocampal volumes [3]. In agreement with the animal studies, childhood trauma in humans is also related to cognitive deficits [16-18].

## II. L-HPA AXIS DYSFUNCTION AND SCHIZOPHRENIA

Walker et al. [49] reported that elevated cortisol secretion predicted psychosis in at risk adolescents who went on to develop the disorder. Furthermore, cortisol levels are positively associated with psychosis in schizophrenia and schizoaffective disorder and with poor performance on (hippocampal-dependent) explicit memory tasks [50]. Dysregulated HPA activity may plausibly contribute to the symptoms and cognitive deficits associated with schizophrenia in a portion of cases. According to a 2010 review of HPA axis function in schizophrenia, mean basal cortisol was significantly increased in 44.2% and significantly decreased in 5.2% of 77 studies [51]. The same review reported that 11 out of 18 studies that measured basal cortisol over at least a 3-hour time interval found abnormal patterns of diurnal variation, with 7 of these studies reporting sustained elevation of cortisol at more than one time point. These results include: increased morning cortisol (3 studies); increased levels in the afternoon (9 studies); elevated evening cortisol (3 studies); and increased levels during the first few hours of sleep (2 studies).

Decreased levels of morning cortisol are also reported, particularly in cases with early trauma, with higher levels/severity of trauma predicting lower morning cortisol [52, 53]. For example, one group of researchers [52] showed that outpatients with at least one moderate rating on the childhood trauma questionnaire (CTQ) exhibited significantly decreased morning cortisol and generally showed decreased 24 hour cortisol levels in comparison with similar outpatients without any moderate or greater levels of trauma. Morning cortisol levels were negatively correlated with emotional and sexual abuse. Furthermore, DST (dexamethasone stress test) nonsuppression is frequently observed in schizophrenia, and often in association with negative [51, 54, 55] and cognitive symptoms [54, 55]. The DST is used to diagnose the presence of increased cortisol states. Dexamethasone is a synthetic steroid that normally suppresses ACTH and CRH secretion through binding to glucocorticoid receptors in the presence of an intact negative feedback system. A review of 85 studies [51] showed DST nonsuppression in 26.9% of schizophrenia patients. While these results provide good evidence for HPA axis dysfunction in schizophrenia, there is clearly some variance among the findings supporting this conclusion (e.g., while the majority of results indicate a hypersuppression of cortisol, others indicate a hyposuppression). Some of these conflicting results may be explained by differences in the frequency and severity of early traumatic or other stressful experiences [51]. For example, researchers **[**56**]** who found a significant negative association between recent stressful life events and cortisol levels in first-episode psychotic patients, including patients with schizophrenia, hypothesized that these results may reflect the exceptionally high amount of stressful life experiences that this group of patients was exposed to. Similarly, a hypofunctioning of cortisol in adulthood might reflect an "over-adjustment" [57] that occurs after protracted exposure to trauma/stress and hyperactivation of cortisol during childhood. These inconsistent results might also reflect individual variations in genetic predisposition, the type of or timing of the trauma, or the effects of other environmental exposures besides the traumatic/stressful experiences.

Sachar [58], whose premature death in 1984 was a major setback for psychiatric neuroendocrinology, first reported that stressful experiences directly preceded the relapse of schizophrenia and that cortisol levels increased by 250% in periods that preceded the worsening of psychotic symptoms, after which cortisol concentrations were reduced to a level between that of pre-episode and recovery. Another clue to the importance of the HPA axis in psychosis includes results indicating that the mechanisms of action of antipsychotic medications include a decrease in ACTH and cortisol levels in healthy subjects [59] and a significant reduction in HPA axis activity and evening cortisol in persons with schizophrenia [60]. The decrease in cortisol levels in schizophrenia is associated with improvement of negative symptoms [61].

Childhood and adolescence, which are phases of pronounced brain development, are considered stress-sensitive periods, during which various brain regions are at increased susceptibility to the effects of stress and trauma [62]. The onset of psychotic symptoms and schizophrenia generally happens in late adolescence and young adulthood. By adolescence, many of the neurocognitive markers associated with the prodrome may have already occurred; these markers include impairment in neuroendocrine and HPA axis functioning and increased sensitivity to certain stressors [20, 63, 64], as well as increased levels of childhood abuse [64]. Walker et al. [65] provided evidence to support the notion that adolescence is a life stage associated with an elevated sensitivity to stress. They reviewed findings indicating that starting at puberty (and during adolescence), HPA axis activity increases, including elevated baseline cortisol levels [65-67] and increased cortisol secretion in response to stress and anger-related states [66]. Furthermore, during this time frame there are also other alterations in steroid hormone activity, like increases in testosterone in males and estradiol in females, [65, 68]. Given the overall pattern of hormonal changes during this life phase, it is understandable why adolescents tend to display affectual and behavioral difficulties, like higher levels of risky behavior, social conflict, distress, embarrassment, and other related behaviors and feelings [65]. Normally, this increase in HPA activity and its associated behaviors remit by adulthood. In some individuals, however, this increased activity may and play a role in psychopathology. Walker et al. [67] utilized a longitudinal design and found that in adolescent males with schizotypal personality disorder (which is often seen in adolescents who later go on to develop schizophrenia), cortisol levels were higher than in controls during the first and follow-up assessment (1.5-2 years after the initial assessment). More importantly, there was a significant association between higher cortisol levels at the first assessment and total schizotypal personality disorder symptoms at follow-up. A similar relationship was also reported between higher cortisol levels at the follow-up assessment and total symptoms at the same assessment. More recently, Walker et al. [69] reported that persons at clinical high risk for psychosis exhibited increased cortisol levels, which were positively associated with symptom severity. These results provide support for the idea that the increases in cortisol and HPA functioning during adolescence may play a role in the expression of genes that lead to psychiatric symptoms in predisposed individuals. Taken alongside the findings indicating that individuals with a predisposition to schizophrenia display a heightened sensitivity/reactivity to everyday events and stressors and that acute onset is often immediately preceded by stressful life events, it seems likely that the natural increases in HPA activity and stress during adolescence may trigger the expression of genes in predisposed individuals that can lead to long-term neurobiological deficits, maladaptive behaviors, and psychopathology.

### *A. The Hippocampus and Schizophrenia*

Abnormalities in the structure, function, and neurochemistry of the hippocampus are consistently found in schizophrenia. Meta-analyses show that schizophrenia is significantly related to decreases in bilateral hippocampal volumes of about 4% [70] and that patients with both first-episode and chronic schizophrenia exhibit significant bilateral volume reductions of the hippocampus [71]. Longitudinal brain imaging studies consistently report volumetric alterations in different brain areas over the course of schizophrenia (in comparison with controls), like reductions in hippocampal [72, 73], whole brain [72], temporal

lobe [73], and frontal lobe [74] volumes, as well as increases in ventricular volumes [72]. Other studies demonstrate that schizophrenia individuals exhibit significantly reduced pyramidal-cell densities in in the CA3 and CA4 regions of the hippocampus, as well as reductions in the CA1 and CA2 regions [75], and significantly decreased spine densities of apical dendrites in the subiculum [76].

Twin studies also demonstrate that hippocampal deficits are related to the disease [77, 78]. A study of 15 pairs of discordant monozygotic twins [78] found smaller hippocampal volume in the affected twin for the left hippocampus in 14 of 15 pairs and for the right hippocampus in 13 of 15 pairs. These results suggest that the observed differences in hippocampal volume are at least partly due to non-genetic exposures and early trauma is a plausible causal factor.

With respect to hippocampal glucocorticoid receptor (GR) levels GR levels, a post-mortem study [79] of schizophrenia, bipolar disorder, depression and comparison subjects only found that significantly decreased GR mRNA levels in schizophrenia in the dentate gyrus and CA1, CA3, and CA4 subregions. The schizophrenia cases also had lower densities of GRs in layers III and IV of the frontal cortex and layer IV of the inferior temporal cortex (relative to controls). Fewer GR receptors in the hippocampus may contribute to the increased stress sensitivity and HPA disturbances observed in schizophrenia.

## III. NEUROBIOLOGY AND SCHIZOPHRENIA: RELATIONSHIP TO THE STRESS CASCADE

### *A. The Neurochemical Substrate*

#### *1) Dopamine:*

Heightened dopamine activity is related to psychosis. Increased dopamine activity is associated with inducing or exacerbating psychotic symptoms; dopamine agonists produce such effects [80, 81] and dopamine antagonists, including typical antipsychotics (which act primarily on dopamine $D_2$ receptors) and atypical antipsychotics (which act in part on $D_2$ receptors), are used to treat psychotic symptoms [81-84].

Notably, glucocorticoid and dopamine levels are positively correlated [85]. In rats, adrenalectomy is linked to a decrease in certain dopamine receptors in the striatum and substantia nigra [86]. Dopamine agonists, including stimulants, elevate HPA activity and cortisol levels [20, 87-90]. Apropos of early stress and trauma, pups exposed to maternal deprivation exhibit elevated dopaminergic activity in the prefrontal cortex (PFC) and amygdala as adults [91]. Similarly, healthy human subjects who reported poor maternal care exhibit increased cortisol and striatal dopamine in response to psychosocial stress, for which dopamine and cortisol levels are positively associated [92].

Long-term increases in glucocorticoid release may occur in response to stress or early trauma, which may then increase dopamine secretion, or perhaps exacerbate already maladaptive dopamine system functioning. In a positive feedback manner, the increased dopaminergic activity can further elevate HPA activity and glucocorticoid release. This positive feedback loop may constitute an important mechanism in the development of psychotic symptoms as well as provide an explanation for the link between early trauma and schizophrenia. Indeed, it has been suggested for quite some time that glucocorticoid release may play a role in schizophrenia by increasing dopaminergic activity [93, 94].

#### *2) Glutamate, GABA, and serotonin:*

Decreased activation of NMDA (N-methyl-D-aspartate) receptors is associated with schizophrenia. In healthy individuals, the administration of ketamine (an NMDA receptor antagonist) induces positive [95-97], negative, and cognitive symptoms [96, 97].

Reductions in the expression of genes involved in glutamate and GABA neurotransmission have been observed in the prefrontal cortex (PFC) in schizophrenia populations [98], as is decreased expression of GAD67, which plays a role in GABA synthesis via catalyzing decarboxylation of glutamate. Since healthy working memory functioning depends in part on normally functioning GABA transmission in the dorsolateral PFC, GABA deficits have been hypothesized to play a role in the working memory deficits commonly observed in schizophrenia [99]. NMDA receptor hypofunction may lead to decreases in GABA activity. Postmortem analyses in schizophrenia show fewer neurons that co-express GAD67 and NR2A (a subunit of NMDA receptors) in the PFC relative to controls [100]. Benes [101] comparably proposed that stress-induced excitotoxicity to inhibitory interneurons in the hippocampus may thereby play a role in leading to schizophrenia.

GABA impairments may also interact with serotonin abnormalities to increase the risk of psychotic symptoms. D'Souza [102] reported that iomazenil, a benzodiazepine antagonist (benzodiazepines are GABA agonists that acts at $GABA_A$ receptors), cooperatively interacted with m-chlorophenylpiperazine (m-CPP), a serotonin agonist, to elevate serum cortisol and induce mild psychotic symptoms in healthy controls. The implication is that GABA impairment may be a risk factor for schizophrenia. Reduced GABA binding to $GABA_A$ receptors interacting with increased serotonergic tone may increase the risk for schizophrenia. Another study [103] showed that when mCPP was given to persons with schizophrenia, cortisol was increased, which in turn increased psychotic symptoms. Olanzapine (an atypical antipsychotic, which in addition to being a dopamine antagonist, also antagonizes serotonin at 5-HT receptors) has been found to significantly inhibit m-CPP-generated release of

cortisol and ACTH in schizophrenia patients [104].

Early evidence for a role of serotonin in the pathogenesis of schizophrenia derived form the discovery that a number of hallucinogens are serotonin agonists that act primarily at the serotonin 5-$HT_{2A}$ receptor [105]. Furthermore, in healthy subjects, the psychosis-like effects of psilocybin are suppressed by ketanserin, a serotonin 5-$HT_{2A}$ antagonist [106]. Taken together, these results suggest that increased binding of serotonin at 5-$HT_{2A}$ receptors may play a role in the development of schizophrenia. Negative symptoms [61, 83, 84] and cognitive deficits [107, 108] are reduced following treatment with atypical antipsychotics, which have comparable antagonism at 5-$HT_2$ serotonin receptors [105], specifically 5-$HT_{2A}$ receptors [109], as at dopamine $D_2$ receptors. Thus, as has been suggested, increased serotonergic activity may play a role in the development of negative and cognitive symptoms.

Animal studies show that stress impacts glutamate, GABA, and serotonin transmission. For example, stress and glucocorticoid release increases glutamate levels in the hippocampus and other brain regions [110, 111] and adrenalectomized rats exhibit altered mRNA levels of different $GABA_A$ receptor subunits (mostly increases) in certain areas of the hippocampus, which are reversed when the rats drink water with low levels of corticosterone [112]. Furthermore, phenytoin (an anti-epileptic agent that hinders excitatory amino acid release and transmission) [113], adinazolam (a benzodiazepine) [114], and tianeptine (a selective serotonin reuptake enhancer, or SSRE) [113, 114] can prevent or reverse stress or corticosterone-induced damage to the hippocampus, such as dendritic atrophy. Thus, it is plausible that early trauma could play a role in leading to some of the neurotransmitter system abnormalities observed in schizophrenia, which may in turn, mediate stress-induced neurotoxic effects to the hippocampus and other brain regions.

### *B. The Neuroplasticity Approach: BDNF and Neurogenesis*

Brain-derived neurotrophic factor (BDNF) is necessary for hippocampal neurogenesis. Furthermore, BDNF levels are diminished by stress. Some studies show reductions in BDNF protein and BDNF mRNA levels in the dorsolateral PFC in schizophrenia [115], as well as significantly decreased levels of BDNF protein and BDNF mRNA in the CA4 region of the hippocampus [116]. BDNF promotes the survival and growth of GABA-ergic neurons via the signaling of its tyrosine kinase receptor (trkB-TK+). In schizophrenia, there are significantly reduced levels of trkB-TK+ in the CA4 region of the hippocampus and GAD67 mRNA levels are reduced in the CA4 region and the dentate gyrus. BDNF also promotes the growth and survival of glutamate neurons and deters glutamate-induced excitotoxicity [117]. Furthermore, BDNF plays a vital role in regard to dopaminergic function in the midbrain; for example, BDNF enables the growth and survival of dopaminergic neurons in the substantia nigra [118] and BDNF in dopamine neurons plays a role in regulating the expression of dopamine D3 receptors in the nucleus accumbens [119]. These findings may help to explain many of the neurotransmitter system abnormalities found in schizophrenia that have already been discussed. As shown in animal studies, stress and corticosterone reduce BDNF mRNA expression in the dentate gyrus [120]; maternal deprivation is associated with similar long-term effects on the hippocampus [121, 122]; and maternal abuse is associated with long-lasting and significantly reduced levels of BDNF mRNA expression in the PFC [123]. Thus, it is feasible that such alterations can mediate the link between early trauma and schizophrenia by producing irregularities in neurotransmitter synthesis and functioning, as well as maladaptive alterations in neural plasticity.

### *C. Epigenetics*

Given the overwhelming amount of research showing the link between genetics and schizophrenia, it has become increasingly important to determine the extent to which environmental and epigenetic factors may contribute to the disorder and exactly what biological mechanisms or systems may be involved. About 85% of the offspring of individuals with schizophrenia don't develop the disorder [124]. Furthermore, the parents of schizophrenia patients actually show much lower rates of schizophrenia than siblings of schizophrenia patients, even though both parents and siblings share virtually identical percentages of genes with the schizophrenia patients with whom they are related [125]. These statistics clearly support a contribution of environment (and/or sporadic mutation) to the development of the disorder. Studies of twins helped to pave the way towards an understanding that schizophrenia is probably produced by a nature-nurture interaction. For example, an analysis of 6 twin studies showed an average (weighted mean) concordance rate of only 39% for monozygotic twins and 10% for dizygotic twins [125].

One epigenetic mechanism that may be linked to schizophrenia is DNA methylation. One group of researchers [126] studied pairs of twins and reported that both twin pairs concordant and discordant for schizophrenia, as well as individuals with psychiatric disorders other than those on the schizophrenia spectrum, exhibited a significant reduction in global DNA methylation (relative to pairs of healthy control twins). These decreases were only significant for male participants. Furthermore, twins that were discordant for schizophrenia exhibited increased levels of methylation of the sex-determining region Y-box containing gene 10 (SOX10) promoter (relative to levels of global methylation).

Animal studies offer similar findings. Weaver et al. [127] demonstrated that the quality of maternal care received by pups is associated with differences in DNA methylation of hippocampal GR genes, which indicates that epigenetic mechanisms may underlie some of the neurobiological differences observed between pups who experience a higher quality of care and those that receive a lower quality of care. Pups of dams exhibiting high amounts of licking and grooming (LG) and arched back nursing

(ABN), analogous to human nurturing behavior, show delimited HPA axis stress responses (in comparison with low LG-ABN pups) and consequently do not have stress-related neurobiological alterations. They also have less behavioral fearfulness/anxiety responses in comparison with the pups of mothers who do not show nurture-related behaviors, along with fewer adrenocorticotropic hormone (ACTH) and corticosterone responses and increased a2 adrenoreceptor density in the locus ceruleus [128, 129]. In a study recently discussed [123], reduced BDNF mRNA expression in the PFC of adult rats exposed to maternal abuse during childhood was explained by the fact that in maltreated rats, BDNF DNA methylation (specifically, increases in BDNF exons IX and IV) lasted from infancy into adulthood.

In humans, childhood abuse is associated with the differential methylation of various promoters [130], including the exon $1_F$ NR3C1 promoter [15]. In humans, the NRC31 gene encodes the GR protein. In this study [15], a post-mortem investigation of suicide victims with exposure to childhood abuse, significant decreases in GR mRNA levels and mRNA transcripts containing the exon $1_F$ NR3C1 promoter may have been a result of this differential methylation. Such changes in DNA methylation may constitute an epigenetic mechanism by which childhood trauma can lead to the neurobiological abnormalities associated with schizophrenia (and with sensitization), which contribute to the development of the disorder.

## IV. SYMPTOMOLOGY OF SCHIZOPHRENIA WITH RESPECT TO STRESS

### *A. Cognitive Impairments*

Stress and early trauma are related to some of the cognitive deficits observed in schizophrenia. One study [131] showed that compared with schizophrenia outpatients with exposure to low levels of childhood trauma or none at all, schizophrenia outpatients reporting moderate or severe levels of childhood trauma displayed significantly worse auditory working memory and episodic narrative memory (specifically, deficits in immediate and delayed recall, but not recognition). In another study [132], individuals with either schizophrenia or schizoaffective disorder and a history of childhood sexual abuse exhibited greater deficits in working memory and information processing speed than individuals with either schizophrenia or schizoaffective disorder and no exposure to childhood sexual abuse. Taken alongside the fact that many of the same or similar cognitive deficits are related to childhood trauma in humans without schizophrenia, as well as to stress/early stress in animals, and that these deficits are found in cognitive abilities that are dependent on brain areas (like the hippocampus and PFC) that are found to be similarly abnormal in both the early trauma/stress and schizophrenia literature, these results suggest that early trauma may play a role in contributing to cognitive impairments observed in schizophrenia. Also, as discussed, DST nonsuppression in individuals with schizophrenia is related to cognitive symptoms.

Most of the cognitive deficits reported in the aforementioned studies are commonly observed in schizophrenia. A meta-analysis [133] of 70 studies found that schizophrenia and memory deficits are significantly related, with schizophrenia patients showing significantly poorer memory performance than comparison groups. Greater deficits in recall, including both verbal and non-verbal memory (immediate and delayed), were reported than for recognition, though both types of memory were significantly impaired. The researchers suggested that this disparity may be due to deficits in retrieval and memory consolidation. Other studies show similar results, including greater deficits in recall than in recognition [134, 135] and greater deficits in encoding and retrieval than in storage [136-138]. A possible explanation for this is that when forming new memories, patients with schizophrenia tend not to employ semantic encoding strategies and other strategic memory processes [136, 138-141], which according to Ranganath et al. [142], suggests an inability to produce “organizational strategies” [140, 142-144]. Furthermore, a few researchers found that the hippocampus may be more involved in recall than in recognition [145-147]. As shown above, hippocampal deficits are consistently linked to schizophrenia, as well as early stress and trauma. Schizophrenia patients also show significant deficits in explicit memory, which is highly dependent on hippocampal functioning, in contrast to implicit memory [148, 1549].

It’s easy to see how deficits in encoding experiences on a deeper, more semantic level, as well as problems with recall, might lead someone to generalize their traumatic experiences and associated memories and feelings onto future experiences and project their feelings and memories of the perpetrators of the abuse or trauma onto other people. Thus, cognitive deficits may increase the likelihood of someone with exposure to childhood trauma to develop psychotic symptoms like paranoid delusions. In fact, deficits in recall-based memory processes are associated with positive symptoms [150]. As Read et al. [26] explain, repeated abuse as a child is “likely to render other people a serious potential threat; a threat that can easily be generalized to anyone or anything that is reminiscent of the perpetrator or the circumstances surrounding abuse.” So, the negative beliefs about other people and the outside world that result from traumatic experiences can produce hypervigilance and an increased sensitivity to psychosocial stressors, which might then develop into paranoid delusions. As mentioned, schizophrenia patients who were exposed to moderate to severe levels of childhood trauma were found to have deficits with episodic narrative memory. Impairment in episodic memory may contribute to the type of hypervigilance described above by impairing an individuals’ capacity to remember the specific details of early traumatic events.

Given that a predisposition to psychosis is related to increased stress sensitivity, it seems likely that neurocognitive deficits may contribute to stress sensitivity by impairing the capacity to adapt and meet the challenges presented by stressful/traumatic experiences. Alternatively, the stressful/traumatic experiences themselves may lead to the neurocognitive deficits and increased stress sensitivity. This alternative is supported by two studies that show that cognitive deficits in schizophrenia

develop during childhood, and are neither present at birth nor subsequent to the onset of illness. In the first, Russell et al. [151] found that childhood IQ in adult patients with schizophrenia were much lower than childhood IQ in the general population and that there were no significant changes in the patients' IQ levels from childhood to adulthood. In the second, Kremen et al. [152] conducted a longitudinal study of 547 subjects and reported that significantly greater than expected reductions in IQ from ages 4-7 (in 10% of the subjects) were correlated with a rate of psychotic symptoms (but not symptoms from other psychiatric disorders) that was almost 7 times higher compared with individuals who didn't show such childhood IQ decline. Thus, it is plausible that childhood trauma can lead directly to cognitive deficits. These deficits may then contribute to stress sensitivity when an individual is faced with subsequent stressors/trauma (in the manner described above). Alternatively a combination of both mechanisms is also a possibility. A third option, as pointed out by Myin-Germeys and van Os [30], is that neurocognitive deficits and increased stress-sensitivity are entirely separate mechanisms that both contribute to psychosis without themselves interacting. Support for this hypothesis comes from a follow-up investigation to a study already discussed [29], in which patients with psychotic illnesses and their relatives were found to exhibit significantly greater stress reactivity/sensitivity to daily events and activities compared with controls. In the follow-up study [153], only the patient group was evaluated. In some situations, cognitive functioning was unassociated to stress reactivity, while in other situations, there was a negative association between these two measures. This suggests that stress-sensitivity and neurocognitive deficits may both contribute to schizophrenia via two distinct causal pathways. However, because neurocognitive deficits are highly related to childhood trauma and dysfunctional neurobiological systems associated with increased stress sensitivity in both healthy individuals and in schizophrenia patients, it seems likely that at least in some patients, neurocognitive deficits and increased stress sensitivity may causally interact on a shared pathway to schizophrenia.

As described, impairment in working memory is related to early stress/trauma in both healthy individuals and in schizophrenia patients. Because of the positive relationship between dopamine and glucocorticoids, it is conceivable that repeated exposure to early trauma could cause elevated dopamine levels (from a normal or abnormally elevated baseline), which in turn could lead to memory deficits in concert with the hippocampal damage from an unrestrained stress system.

### *B. Positive Symptoms*

Victims of childhood abuse exhibit high rates of positive symptoms, particularly hallucinations, as well as delusions (but to a lesser degree). In a review, Read et al. [26] reported a significant association between childhood abuse and hallucinations in the majority of studies evaluated. They found a significant or trend relationship between delusions and child abuse in just under half of the studies that measured these factors. Only one study reviewed found a significant relationship between thought disorder and child abuse, 4 reported non-significant trends, and 9 reported no association. An association of high levels of early trauma with positive symptoms has also been observed in patients with first-episode schizophrenia [27]. Another study already reviewed [23] found a dose-response relationship between childhood abuse (but not neglect) and positive symptoms in patients with psychotic illness, their siblings, and healthy controls. An association between verbal auditory hallucinations and childhood sexual and emotional abuse in both adults with and without a psychotic disorder has also been reported [154]. Also, in adolescents and young adults at clinical high risk for psychosis, early trauma is significantly associated with the severity of attenuated positive symptoms [155]. However, after dividing the entire cohort into ethnic subgroups (Caucasians and minorities), this relationship only remained for the minority group, which suggests that childhood trauma may affect some ethnic groups more adversely than others, though more studies are required.

Whitfield et al. [156] conducted a survey with over 17,000 participants and found a significant graded relationship between early adverse experiences and hallucinations, with the risk of experiencing hallucinations being 1.2-2.5% higher for those who experienced early adverse experiences compared with those who didn't. Individuals who experienced 7 or more early adverse experiences were 5 times more likely to report hallucinations compared with those who didn't have such early experiences.

Neuroticism is linked to the positive symptoms of schizophrenia. For example, neuroticism is associated with the severity of delusions in schizophrenia patients [157]. The degree of neuroticism displayed by an individual is a good indicator of his/her vulnerability to stress and emotional disharmony; neuroticism is classified by traits such as emotional instability and elevated stress sensitivity [30, 158], which are core constituents of the mechanism of stress sensitization. One study [158] reported that individuals with schizophrenia exposed to childhood sexual abuse exhibited significantly higher levels of neuroticism and significantly more deficits with social and occupational functioning than individuals with the same diagnosis but without exposure to early sexual abuse.

Given the fact that increased dopaminergic transmission is strongly linked with the development of positive symptoms, and that glucocorticoids and dopamine function have a positive relationship, it is plausible that early trauma and stress (and resultant increase in glucocorticoid levels) can cause the type of dopaminergic hyperactivity associated with positive symptoms. More support for this hypothesis comes from findings already discussed, including a positive association between cortisol levels and positive symptoms in patients with schizophrenia or schizoaffective disorder [50] and increased cortisol levels predicting the development of psychosis in at risk youth [49].

Corcoran et al. [159] studied a group of at risk adolescents with attenuated positive symptoms who were undergoing treatment during Phase 1 of the Recognition and Prevention (RAP) Program and found that cortisol release was related to

suspiciousness, but not to overall positive symptom severity. Both cortisol and suspiciousness were separately associated with impaired tolerance to normal stress. Based on these results, it is possible that increased HPA activity and sensitization to stress are associated with certain positive symptoms but not others. Also, as the authors suggest, the correlations found in this study may only pertain to individuals with prodromal symptoms who don't actually go on to develop psychotic disorder. A longitudinal study [160] found that youths at clinical high-risk for schizophrenia exhibited increased stress sensitivity, which was associated with positive symptoms over time. However, neither total recent life stress nor stress sensitivity were predictive of the development of psychosis.

Re-experiencing symptoms in PTSD, including flashback memories, and intrusive and distressing thoughts and images, may be conceptualized as additions to normal experiences, the positive symptoms of schizophrenia and other psychoses, including hallucinations and delusions [161]. The increased arousal symptoms in PTSD include hypervigilance to threat, which is also similar to some positive symptoms of schizophrenia [162, 163]. Vietnam combat veterans with PTSD have been found to exhibit high rates of psychotic symptoms [164, 165]. As might be expected, childhood trauma is a risk factor for PTSD [166]. Findings from studies of individuals with PTSD and exposure to childhood trauma show: significantly increased levels of 24-hour urinary free cortisol and increased levels of urinary dopamine and norepinephrine [167]; cortisol levels and severity of PTSD symptoms at baseline in children are significant predictors of decreased right hippocampal volumes 12-18 months later [168]; measures of cortisol levels are negatively associated with explicit memory [169]; significantly reduced left hippocampal volumes; and significantly reduced right hippocampal volumes and deficits in verbal memory associated with the hippocampal reductions [170]. These results suggest that increased HPA activity, alongside the corresponding hippocampal and memory deficits (which are associated with early stress and sensitization, as well as with schizophrenia) could potentially play a role in leading to positive symptoms. In contrast with the results mentioned above, PTSD is frequently associated with average or even reduced levels of cortisol and increased inhibition of HPA stress response [171]. However, the studies of persons with PTSD exposed to reminders of traumatic events [172, 173] demonstrate elevated cortisol and HPA responses in comparison with controls. Thus, as Yehuda points out, it is not necessarily true that individuals with PTSD display lowered HPA and stress responsiveness [171].

### *C. Negative Symptoms*

The review by Read et al. [26] reported a paucity of studies investigating the potential relationship between negative symptoms and child abuse. 9 studies were found in total, with 3 reporting high rates of negative symptoms in victims of child abuse (though these studies didn't use a control group) compared with 6 studies that found no relationship between negative symptoms and child abuse. Some studies already mentioned reported that early trauma is unrelated to negative symptoms in populations with psychotic disorders [23], including first-episode schizophrenia [27], and in adolescents and young adults at clinical high risk for psychosis [155]. Interestingly, a longitudinal study already mentioned [160] found that increased stress sensitivity was related to negative symptoms over time in youths at clinical high risk for schizophrenia, which may provide some evidence for the hypothesis that early traumatic experiences contribute to the development of negative symptoms via elevating stress sensitivity. Regardless of whether this is the case or not, because the same association was found between positive symptoms and stress sensitivity (as above), the authors concluded that impaired stress tolerance is a common characteristic of psychosis risk syndrome.

In a study of patients with paranoid schizophrenia, or with other psychiatric illness, Vogel et al. [174] found across diagnoses that childhood trauma was significantly and positively associated with negative symptoms, and with PTSD and dissociation, which was itself associated with dissociation. Schizophrenia was correlated with early neglect, while non-psychotic disorders were correlated with abuse. Based on these results, the researchers suggested that childhood neglect and abuse might lead to different results in schizophrenia and other disorders. Early trauma might lead to deficits in important abilities (like cognitive, emotional. social, and motivational functioning), which "map onto the construct of negative symptoms." Thus, negative symptoms in schizophrenia and other disorders may be indirectly linked to childhood trauma.

Serotonergic hyperactivity may play a role in the development of negative symptoms. In support of this hypothesis, one study already discussed showed that not only did treatment with risperidone alleviate negative symptoms and cause a significant decrease in cortisol in schizophrenia patients, but the reduction in cortisol was related to the reduction in negative symptoms [61]. Increased dopaminergic activity may also play a role in the development of negative symptoms. One group of researchers [175] reported that among a group of healthy subjects at increased risk for psychosis, those who displayed negative symptoms (but not those who displayed subclinical positive symptoms) exhibited a significant increase in striatal dopamine release in response to a psychosocial stressor, which may be linked to frontal lobe dysfunction, and which suggests a relationship between stress-induced dopaminergic hyperactivity and negative symptoms. In light of the fact that increased dopamine is generally related to positive symptoms, the authors suggested that these results may be explained by findings indicating that a genetic predisposition to schizophrenia (as studied in relatives of schizophrenia patients) is associated with increased levels of subclinical negative, but not positive, symptoms [176, 177]. Finally, this study also showed that low maternal care was significantly associated with increased dopamine for all subjects, indicating that early stress and subsequent increases in dopamine may contribute to the development of both positive and negative symptoms.

Depressed mood, anhedonia, and asociality, are considered negative symptoms, which are often seen in schizophrenia [178-180]. Depression is associated with high rates of early trauma [181-183] and also with HPA axis hyperactivity, like high levels of cortisol [184, 185]. Particularly high rates of cortisol and HPA axis dysregulation are found in patients with psychotic depression, as evidenced by higher rates of DST nonsuppression [186] and 24-hour cortisol levels [187]. As mentioned, high rates of DST nonsuppression are also found in schizophrenia and are associated with negative symptoms. These results suggest that increased cortisol and a lack of HPA negative feedback (which are associated with early stress and sensitization, as well as with schizophrenia) could potentially play a role in leading to negative symptoms.

Some deficits in behavior, which are associated with avoidance in PTSD and negative symptoms in schizophrenia, include blunted affect, diminished emotional range, and social withdrawal [161-163]. Vietnam combat veterans with PTSD have been found to exhibit certain negative symptoms, like anhedonia [164]. Because individuals with PTSD and early trauma exposure share similar sensitization-related neurobiological abnormalities with people with schizophrenia, this suggests that early trauma may lead to schizophrenia via these alterations.

Based on some of the similarities in negative symptoms seen in schizophrenia and PTSD, Stampfer [163] proposed that having a psychotic disorder is in itself a traumatizing experience and that this traumatic experience is what may lead to the development of negative symptoms. Expanding on this theory, Harrison and Fowler [162], reported that in individuals recovering from schizophrenia, both the avoidance of traumatic memories related to having schizophrenia and being hospitalized, as well as a lack of specificity in autobiographical recall, were significant predictors of negative symptoms. These results led them to conclude that individuals with psychotic disorders who try to avoid the traumatic memories associated with having the disorder and being hospitalized tend to recall more overgeneral (and less specific) autobiographical memories, and in effect develop greater negative symptoms.

## V. CONCLUSIONS

In sum, there is a great deal of evidence to support the hypothesis that early trauma can play a role in the pathogenesis of schizophrenia, including in the development of the hippocampal abnormalities, neurocognitive deficits, glucocorticoid induced elevations in dopamine, and symptoms associated with the disorder. Sensitization-related effects (like increased cortisol levels, abnormal patterns of diurnal cortisol rhythms, damage to the hippocampus, and decreased GR/GR mRNA levels in the hippocampus) are frequently observed in samples of cases with schizophrenia in association with early traumatic experiences, complementing the findings in animals and from those in the general population with exposure early stress/trauma. These neurobiological alterations may be accounted for by certain epigenetic effects that appear to be related to early stress/trauma, like altered DNA methylation of different genes (including BDNF genes or hippocampal GR genes). The experience of early trauma may serve to increase stress sensitivity and HPA activity in individuals with a genetic predisposition to schizophrenia such that the normal increases in hormonal and HPA activity during adolescence might cause the alterations in gene expression necessary to lead to the development of disorder.

Positive symptoms appear to be more associated with childhood trauma than any of the other symptoms of schizophrenia. High rates of positive symptoms are found in victims of early trauma. Hyperactivation of dopamine is especially related to positive symptoms. Because glucocorticoid release modulates and increases dopamine functioning, it is likely that increased glucocorticoid activity, as a result of early trauma and stress, could elevate dopamine levels, or act upon already maladaptive dopamine circuits, to induce positive symptoms. There is less evidence for a connection between early trauma and negative symptoms. Only a few studies have reported a relationship between these two factors, though this area remains relatively understudied. DST nonsuppression (and thus, elevated cortisol levels and decreased inhibition of the HPA axis response) is related to negative symptoms. There appears to be a link between early trauma and cognitive deficits. These deficits are found for cognitive abilities that are dependent on the PFC and hippocampus, which are found to have structural and functional impairments in both animals and humans subject to early trauma/stress, as well as in individuals with schizophrenia. HPA axis dysregulation, as well as the dysregulation of certain neurotransmitter systems (that can be modulated by glucocorticoids in response to stress), are related to such cognitive deficits and are also observed in individuals with schizophrenia. Taken together, in accordance with the glucocorticoid cascade hypothesis, it is feasible that in response to early trauma, excessive glucocorticoid production (with resultant modifications in neurotransmitter release) causes neurotoxicity in the hippocampus, which leads to learning and memory impairments, as well as psychotic symptoms. Cognitive deficits and negative symptoms may lie on a separate causal pathway (to schizophrenia) from increased stress sensitivity and positive symptoms (with each pathway being associated with distinct biological mechanisms, like serotonin hyperfunction for the negative/cognitive pathway and dopamine hyperfunctioning for the stress/positive pathway). However, the evidence suggests that at least in some individuals, increased stress sensitivity and cognitive impairments might be two links of the same chain, with cognitive impairments worsening an already elevated stress sensitivity in individuals predisposed to psychosis by impairing their ability to cope with traumatic/stressful experiences, or with early traumatic experiences leading directly to the cognitive deficits, or a combination of both. It is also possible that cognitive deficits contribute to both the development of positive and negative symptoms. In sum, all of these potential pathways could hypothetically either stem out from or be exacerbated by the experience of early trauma.

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