Schizophrenia Research 213 (2019) 1–5

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Editorial

Advances in the neurobiology of stress and psychosis

Vijay A. Mittal [a, *], Elaine F. Walker [b]

[a] Department of Psychology, Northwestern University, 2029 Sheridan Road, Swift 202, Evanston, IL 60208, USA
[b] Department of Psychology, Emory University, 36 Eagle Row, Atlanta, GA, USA 30322

ARTICLE INFO

Article history:
Received 27 August 2019
Accepted 27 August 2019
Available online 28 September 2019

Keywords:
Stress
Psychosis
Genes
Neurobiology
Hormones
Animal model
Schizophrenia

The historical link between stress and psychosis may be traced back to a highly cited (> 3184) paper published by Joseph Zubin and Bonnie Spring in 1977, which had a significant impact on the trajectory of schizophrenia research. The central thesis of the paper is that "*challenges elicit a crisis in all humans, but depending on the intensity of the elicited stress and the threshold for tolerating it, that is, one's vulnerability, the crisis will either be contained homeostatically or lead to an episode of disorder.*" The most salient impact of the paper was to move the field closer to reconciling the competing theoretical assumptions about etiology that dominated the field at the time; essentially, the nature/nurture debate about the origins of serious mental illness (Grinker et al., 1971). In subsequent decades the word "stress" became increasingly common in the literature on schizophrenia spectrum disorders, and diathesis-stress conceptualizations became widely accepted. Assumptions about socio-environmental and biological etiologic factors were no longer considered incompatible.

It is of interest, however, that the following words do not appear in the paper; *hypothalamus, pituitary, cortisol (or any other hormone), HPA axis, brain (or the name of any brain region), or neurotransmitter (or the name of any neurotransmitter)*. The absence of these terms reflects our limited understanding of stress biology in 1977, as well as the persistence of the implicit assumption of boundaries between psychosocial and biological determinants of psychopathology. Since the 1970s, our scientific understanding of diathesis-stress mechanisms has advanced dramatically.

The articles comprising this Special Issue of Schizophrenia Research on stress and psychosis reflect these burgeoning scientific advances and also exemplify the breadth and depth of the evolving research on this topic. They address topics at all levels of analysis from stress-sensitive neuromolecular processes, to the effects of life stress/trauma on brain structure and cognition. While it is clear that there is much we do not yet understand, there is little doubt that there have been major advances in research on stress and schizophrenia. In this editorial, we take the opportunity to point out some of the challenges in the field while highlighting and integrating the advances represented by the articles in this Special Issue. Lastly, we consider the new questions generated by those emerging research findings.

At the onset, it is important to acknowledge the nonspecificity of stress exposure and stress neurobiology as risk factors for mental illness. While some aspects of vulnerability to psychosis, versus other psychiatric disorders, may be unique (e g., polygenic risk profiles or functional connectivity, etc.), there is no compelling evidence that stress-sensitivity or HPA dysfunction is unique to psychosis risk. It should also be acknowledged that clinical research on stress involves multiple issues and challenges. (For a general discussion, see Pruessner et al., 2017)

In this Special Issue, the review article by Subramaniam et al. (2019) addresses one of the thorniest challenges: the effects of psychotropic medication on the HPA axis. Both antidepressants and antipsychotics tend to be associated with reductions in basal and post-dexamethasone-CRH (DEX/CRH) cortisol, while psychostimulants are reported to be associated with an increase or no change in basal cortisol. There also is evidence that pretreatment cortisol levels are predictive of the treatment response to antidepressants and antipsychotics. While these effects may obscure the role of stress and the HPA axis in illness onset and course, they also have the potential for shedding light on the mechanisms of action of psychotropics and heterogeneity among patients in the determinants of treatment response.

The papers in this Special Issue highlight the developmental implications of stress for schizophrenia and other psychoses across the lifespan. As described by Ellman et al. (2019), previous human studies have demonstrated a link between maternal prenatal stress exposure and risk for psychopathology in offspring. These investigators extend those findings and present data from a prospective birth-cohort study that bear on the biological mediators of this relation; cortisol levels from maternal sera during pregnancy were found to be specifically associated with fetal growth

* Corresponding author.
E-mail addresses: E-mail address: vijay.mittal@northwestern.edu (V.A. Mittal). psyefw@emory.edu (E.F. Walker).

https://doi.org/10.1016/j.schres.2019.08.030

retardation among males who subsequently developed schizophrenia spectrum disorders (SSD). Thus, fetal growth delay, which has previously been shown to be related to prenatal cortisol elevations *and* later risk for SSD, appears to mediate the relationship.

At the neurobiological level, Saunders et al. (2019) conducted a sophisticated meta-analysis to examine pituitary volume in multiple populations at high-risk for psychosis, including CHR, family history of psychosis (FHx), schizotypal personality disorder (SPD), individuals with psychotic-experiences (PEs) and healthy controls. Despite reduction in whole brain volume, both the SPD and PE groups had significantly larger pituitary volume than healthy controls, and the trend was in the same direction for CHR and FHx. Further, high risk subjects who later transitioned to psychosis showed larger pituitary volume than those who did not transition. Because pituitary volume enlargement is assumed to be linked with HPA axis dysregulation, these findings add to the evidence that stress neurobiology is relevant as a vulnerability factor, as well as an important factor in the early course of psychosis.

Several papers in this Special Issue explore the relation of stress exposure with symptoms and/or biomarkers. Vaessen et al. (2019) used experience sampling methodology (ESM) over six consecutive days to measure emotional recovery from daily stressors in patients with chronic psychosis (CP), early stages of psychosis (EP: CHR or first episode), and healthy volunteers (HV). Following stressors, the EP group showed a delayed recovery from negative affect and suspiciousness when compared to the HV and CP groups, but there were no differences in recovery between HV and CP. While the absence of a difference between the HV and CP groups may indicate that stress-sensitivity declines after years of illness, the authors suggest that it may also be a consequence of treatment effects in that the CP patients had a higher rate and longer history of both medication and therapy.

Exposure to stress/adversity may also leave a signature on the brain. Focusing on bullying as a stressor for CHR youth, Vargas et al. (2019) used magnetic resonance imaging (MRI) to examine volumes in regions of interest (ROIs) associated with sensitivity to environmental stress. Confirming previous reports, they found that CHR individuals were exposed to more bullying than healthy volunteers, and bullying was associated with depressive symptoms. The CHR group had smaller orbitofrontal cortex and hippocampal volumes, and exposure to bullying was associated with lower medial OFC volumes in the CHR and healthy groups. This is of particular interest given the point made by Zubin and Spring (1977), as these data suggest that stress is impacting youth across groups, but in the case of CHR individuals, the deleterious effects are greater. Along similar lines, LoPilato et al. (2019) examined the volumetric correlates of two categories of childhood adversity, threat and deprivation, in CHR youth. The distinction between threat and deprivation was based on previous evidence that these two classes of adversity may have different effects. The results indicate that childhood deprivation (e.g., poverty, neglect), but not threat (e g., emotional, physical, or sexual abuse), was associated with smaller global cortical and right hippocampal volume in CHR youth. While the two classes of adversity are positively correlated, these results suggest more fine-grained distinctions among subtypes of stress/adversity exposure may be informative.

Consistent with the point made by Zubin and Spring (1977), understanding continuous and discrete boundaries surrounding how stress affects normative and clinical populations may yield critical clues to pave the way forward. In this light, one innovative approach is to examine how exposure to adversity in healthy individuals is related with the cognitive tendencies, such as abnormalities in the processing of salience, and patterns of corticostriatal connectivity associated with psychosis. The study reported by McCutcheon et al. (2019) compared healthy adults with and without exposure to adversity (e g., migration, emotional, or physical abuse) and found that the exposed group showed reduced explicit adaptive salience scores, increased aberrant salience scores, and increased corticostriatal connectivity between the ventral striatum and cortical regions implicated in salience processing. All of these have been previously observed to be associated with psychosis. Finally, shedding light on mechanisms, analysis suggested that differences in connectivity mediated the relation of stress with salience scores. Again, these results indicate that some of the adverse effects of stress are nonspecific and can be observed in healthy individuals.

Advances in techniques for the measurement of cortisol offer new approaches for the study of stress and psychosis. In an innovative study, Aas et al. (2019) measured hair cortisol, an approach that allows for a unique temporal perspective of stress reactivity, and childhood trauma exposure in healthy controls and patients with schizophrenia or bipolar disorder. They found that patients with a history of childhood maltreatment had higher hair cortisol compared to both healthy controls and patients without exposure to maltreatment. Patients with higher HCC also had poorer working memory performance. Cherian et al. (2019) also present evidence that the cognitive deficits associated with psychosis are partially determined by heightened HPA activity. Comparing healthy controls to patients with schizophrenia or major depression with psychosis, both patient groups performed more poorly than the healthy controls across a variety of cognitive measures, and performance tended to be inversely correlated with plasma cortisol. Patients with major depression and psychosis had higher evening cortisol levels than did the schizophrenia group and healthy controls, although, as would be expected, a higher proportion of the schizophrenia group was on antipsychotic medication.

It is well established that stress exposure and its biological sequelae have implications for neuroinflammatory processes, and the mechanisms involved are the subject of investigation. In previous studies using PET, Romina Mizrahi and her group (Tseng et al., 2017) found evidence of disrupted PFC dopamine mediated stress regulation in schizophrenia, but not in CHR patients. In this special edition, these investigators (Schifani et al., 2019) present novel data, obtained in vivo, on the relation of stress-induced PFC dopamine release with hippocampal TSPO expression (a neuroimmune marker) in a combined sample of antipsychotic-free psychosis spectrum (CHR and schizophrenia) patients. Stress was induced with the Montreal Imaging Stress Task and the control condition involved performing a Sensory Motor Control Task. The study revealed that stress-induced dopamine release in the PFC was inversely related with TSPO expression in the hippocampus, suggesting interactions between these two brain regions via dopamine and immune activation. The novel methodology and findings suggest new avenues for exploring the interplay between stress and immune function.

Lee et al. (2019) move to the cellular level of analysis to shed light on the mechanism(s) mediating the relation of stress with psychosis. As they note, the neurobiological response to stress is determined not only by levels of HPA secretatagogues but also by a myriad of other factors, including individual differences in levels of glucocorticoid receptors (GR) and their binding proteins. Stress-signaling mRNA levels for five protein coding genes associated with GR function (NR3C1, FKBP5, FKBP4, PTGES3 and BAG1) were measured in peripheral white blood cells of schizophrenia patients and healthy controls. Compared to controls, medicated (antipsychotics and antidepressants) patients showed increased FKBP5 mRNA, and decreased FKBP4 and PTGES3 mRNA. This partially replicates findings from postmortem studies and illustrates the importance of examining glucocorticoid receptor (GR) characteristics in order to understand the neurobiology of stress in serious mental illness.

As described above, neurobiological and cognitive correlates of stress exposure and HPA activity have been observed in numerous studies of both patients and healthy individuals. But establishing

causal relations in research on humans is constrained by limits on experimental control. Animal models offer the advantage of experimental manipulation, as well as more fine-grained examination of neuromolecular processes. One of the processes implicated in the adverse effects of stress and heightened HPA activity is redox dysregulation induced oxidative stress. In their mouse model, Cabungcal et al. (2019) in Switzerland focus on cortical inhibitory neurons that express parvalbumin (PV) because they are particularly susceptible to oxidative stress and have been implicated in the cognitive deficits associated with schizophrenia. They tested mice with genetically compromised glutathione synthesis (Gclm KO mice); specifically transgenic mice carrying a germ-line deletion of the modulatory subunit (GCLM) of the glutamate-cysteine ligase holoenzyme which is the rate-limiting enzyme in the glutathione (GSH) biosynthesis pathway. The resultant reduction of brain GSH levels leads to an increased susceptibility to oxidative stress. The study revealed PV cell deficits in Gclm KO mice, that were apparent first in the thalamic reticular nucleus (postnatal day 20 or P20), then followed by the amygdala at P40, then in the lateral globus pallidus and ventral hippocampus at P90, and finally the anterior cingulate cortex at P180. They conclude that PV neurons are developmentally susceptible to oxidative stress and that that this can disrupt circuit maturation and functional connectivity. In their discussion, the authors go on to speculate on the developmentally moderated interplay of oxidative stress with environmental stressors and perturbation of the HPA axis in cortical maturation.

Developmental moderation is also a prominent component of the prenatal methylazoxymethanol acetate (MAM) rodent model discussed by Gomes et al. (2019). MAM is a mitotoxin and DNA alkylating agent, and fetal exposure to MAM leads to abnormal DNA methylation in the offspring. As a result, the MAM offspring are characterized by heightened stress reactivity and anxiety before puberty, and a subsequent hyperdopaminergic state. The pharmacological treatment of prepubertal anxiety prevented dopamine dysfunction in adulthood. When normal rats are exposed to strong stressors during early development, the schizophrenia-related phenotypes of MAM rats are manifested. But when applied during adulthood, the stress paradigm only produced short-term depression-related deficits. Thus developmental disruption can confer increased susceptibility to subsequent stress at critical developmental periods. The hippocampus plays an important role in regulating dopamine, is particularly susceptible to stress, and the maturational course of its PV interneurons may play a role developmental changes in stress vulnerability.

As with other areas of clinical research on etiology, establishing causality is a formidable challenge. For example, the relations of stress exposure with biomarkers may reflect preexisting biological vulnerabilities that increase the likelihood of stress exposure. This is true for the associations between stress exposure and brain structure; volumetric reductions in cortical and subcortical regions may predate stress exposure, but increase its subsequent likelihood. Similarly, heightened cortisol secretion and other indicators of HPA dysfunction may be a consequence of psychiatric symptoms, rather than a causal factor. Nonetheless, controlled experiments with rodents have clearly demonstrated the adverse causal effects of stress exposure on brain structure and connectivity, and the presence of critical developmental periods (Magalhães et al., 2018). The animal models discussed in this edition offer highly plausible neurobiological mechanisms to account for these effects. Further, recent research on rodents has revealed biomarkers of vulnerability to stress. Magalhães et al. (2018) divided stressed rodents into high responders (higher corticosterone release and behavioral disruption) and low responders (lower corticosterone and less behavioral disruption). They found that some stress-induced brain changes (i.e., reduced hippocampus) were similar in high and low responders, but others (e.g., in orbital cortex, the VTA, the hypothalamus, and pontine reticular nucleus) were specific to high or low responders. Finally, examination of functional connectivity before any exposure to stress revealed differences between high and low responders in a brainstem–limbic network connectivity. Similarly, there are likely etiologic subtypes of psychosis that vary with respect to stress-sensitivity.

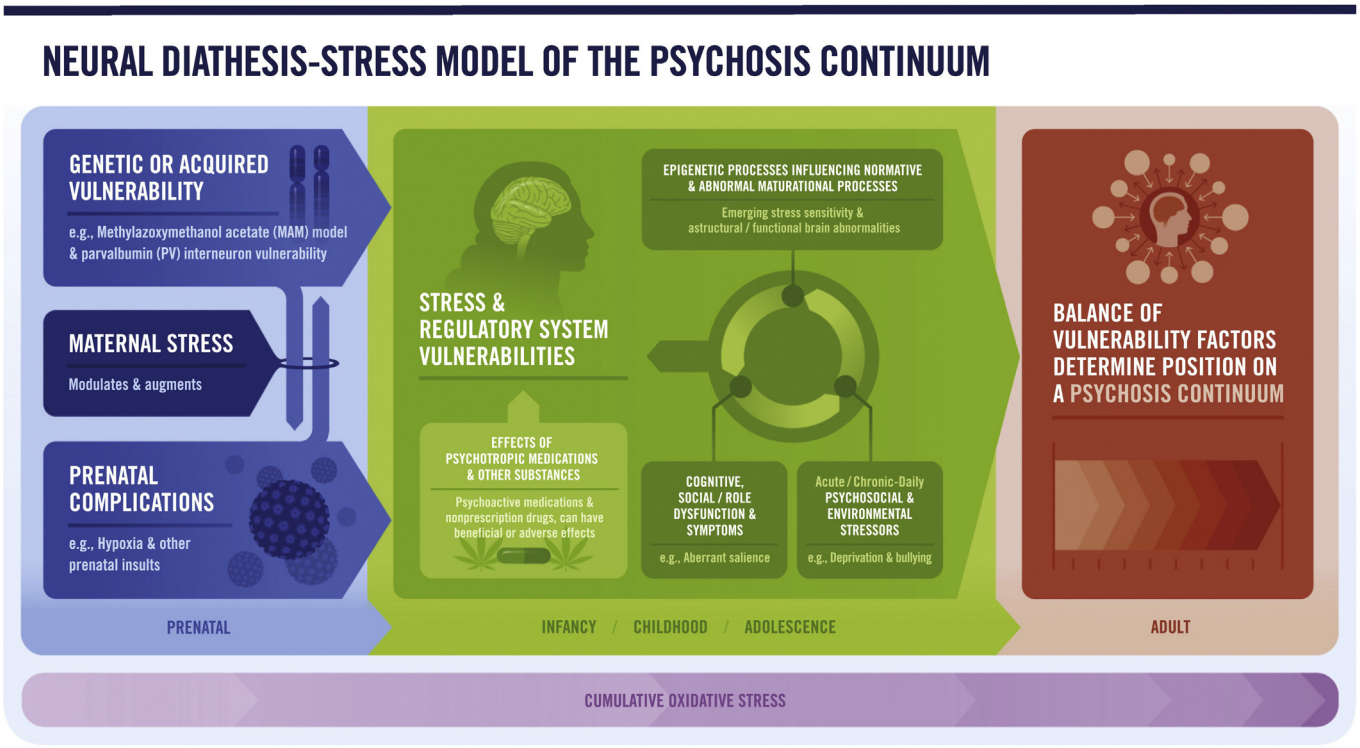

Fig. 1. Recent advances in the field of stress neurobiology enrich a neural diathesis-stress conception of the psychosis continuum. The model incorporates increased complexity and as a result, continues to show promise for explaining pathophysiology, producing new research questions, and developing novel biomarker and precision medicine applications.

In 1977, when Zubin and Spring discussed the interplay between stress and vulnerability in the etiology of psychosis, there were no substantive bodies of scientific literature on links between psychosocial stress and biomarkers of vulnerability. But by 1997, our understanding of stress neurobiology had burgeoned, and it provided a basis for a "neural diathesis stress" model that postulated mediating neural mechanisms in the interplay between stress and vulnerability (Walker and Diforio, 1997). Subsequently, as findings accumulated, the model was modified to incorporate more details of these mechanisms (Walker et al., 2008), as well as scientific evidence generated by new methods and techniques (Pruessner et al., 2017). The lines of investigation presented in this Special Issue demonstrate how continued incorporation of developmental science, as well as advances in techniques for measuring stress exposure, HPA activity, real-time behavior, biomarkers, and in vivo brain structure/function, have revolutionized the field. They also highlight the likely heterogeneity among individuals in the cascade of events that determine their risk for psychosis onset.

In Fig. 1, we depict the factors and processes that are featured in these articles, beginning with the prenatal period and extending to adulthood, when additive and interactive effects determine the individual's position on the psychosis continuum. A host of prenatal factors has the potential to alter fetal neural development. In some cases, inherited and acquired genetic risk factors may play a primary, direct role in determining the individual's ultimate position on the continuum. But for others, genetic vulnerabilities may increase risk by conferring greater sensitivity to other factors and contribute primarily in interaction with them. It appears that maternal stress exposure can set off a neurobiological cascade that has deleterious effects on fetal brain development; it is plausible that genetic factors partially determine sensitivity to this cascade. Maternal stress also heightens the likelihood of prenatal complications that can further compromise fetal brain development. This 'programming' of fetal vulnerability then plays out in interaction with a range of postnatal factors. Many of these factors have their effects by further altering stress sensitivity. For example, there is evidence that both prescription and recreational drugs can alter HPA function.

Similarly, glucocorticoid release triggered by trauma and stress has the potential to influence epigenetic processes that govern neuromaturation. As discussed by several authors in his Special Issue, there is now significant evidence that early childhood and adolescence are each critical periods of stress sensitivity. Therefore normative stressors during sensitive periods, deficient coping or support, abnormalities in stress neurobiology, or interactions among these factors have the capability to drive abnormal brain development.

In addition, as illustrated in Fig. 1, stress and HPA activation can trigger self-perpetuating feedback loops; the adverse influence of previous exposures increases the likelihood of, and sensitivity to, subsequent exposures. As shown by several studies in this Special Issue, stress is linked with cognitive, social, and role dysfunction, as well as the emergence and subsequent maintenance of symptoms. Functional deficits, in turn, can compromise the individual's ability to cope with later stress exposure, thereby amplifying its effects. Moving from the prenatal period through childhood, adolescence and early adulthood, the cumulative adverse effects of exposures exacerbate oxidative stress that can impair cortical maturation and connectivity.

As noted above, there is substantive evidence for etiologic heterogeneity in psychosis. One clear indication of this is the modest variance in psychiatric phenotypes accounted for by schizophrenia polygenic risk scores (PRS), with a recent estimate of 6% of the variance, based on aggregated reports (Mistry et al., 2018). Of course, the PRS does not index the contribution of mutations, rare SNPs, or the myriad of prenatal and postnatal factors, including stress, which determine psychosis risk. It is likely that individual differences in stress exposure and HPA function are also accounting for a significant portion of the variance. Thus, identifying biomarkers associated with stress-sensitivity may shed light on etiologic subtypes and aid in tailoring treatments to subgroups of patients most likely to respond.

From the standpoint of etiological models, the domain of stress neurobiology is somewhat unique in that provides a clear interaction point among key driving forces such as development, psychosocial stressors, and biological vulnerability for psychosis. This pivotal role has attracted growing attention over the past few decades from those aiming to identify, understand, and treat disorders such as schizophrenia. Dovetailing these developments is a growing understanding that effectively mapping this intersection is a deeply nuanced and highly complex undertaking. Fortunately, the innovation and capabilities of contemporary research methods, as well as the integration of diverse conceptual frameworks, has spurred a remarkable body of work and prompted the field to approach increasing complexity demanded by goals such as explaining mechanisms, discovering biomarkers, informing individualized medicine, and inspiring the development of more targeted treatments. As a result, we have seen significant progress since the seminal 1977 paper by Zubin and Spring. The work in this Special Issue speaks to the promise of continuing to build our understanding of stress and psychosis, and highlights some clear paths forward for the years to come.

Contributors

Mittal and Walker worked together to develop and draft this manuscript.

Role of funding source

NA.

Declaration of competing interest

None to report.

Acknowledgement

NA.

References

Aas, M., Pizzagalli, D.A., Laskemoen, J.F., Reponen, E.J., Ueland, T., Melle, I.…, , 2019. Elevated hair cortisol is associated with childhood maltreatment and cognitive impairment in schizophrenia and in bipolar disorders. Schizophr. Res. 213, 65–71.

Cabungcal, J.H., Steullet, P., Kraftsik, R., Cuenod, M., Do, K.Q., 2019. A developmental redox dysregulation leads to spatio-temporal deficit of parvalbumin neuron circuitry in a schizophrenia mouse model. Schizophr. Res. 213, 96–106.

Cherian, K., Schatzberg, A.F., Keller, J., 2019. HPA axis in psychotic major depression and schizophrenia spectrum disorders: cortisol, clinical symptomatology, and cognition. Schizophr. Res. 213, 72–79.

Ellman, L.M., Murphy, S.K., Maxwell, S.D., Calvo, E.M., Cooper, T., Schaefer, C.A., Bresnahan, M.A., Susser, E.S., Brown, A.S., 2019. Maternal cortisol during pregnancy and offspring schizophrenia: influence of fetal sex and timing of exposure. Schizophr. Res. 213, 15–22.

Gomes, F.V., Zhu, X., Grace, A.A., 2019. Stress during critical periods of development and risk for schizophrenia. Schizophr. Res. 213, 107–113.

Grinker, R.R., Albee, G.W., Schachter, J., Garmezy, N., Thrasher, R.H., Mensh, I.N., 1971. Emerging conceptions of mental illness and models of treatment. Prof. Psychol. 2 (2), 129.

Lee, C.H., Sinclair, D., O'Donnell, M., Galletly, C., Liu, D., Weickert, C.S., Weickert, T.W., 2019. Transcriptional changes in the stress pathway are related to symptoms in schizophrenia and to mood in schizoaffective disorder. Schizophr. Res. 213, 87–95.

LoPilato, A.M., Goines, K., Addington, J., Bearden, C.E., Cadenhead, K.S., Cannon, T.D., …, Perkins, D.O., 2019. Impact of childhood adversity on corticolimbic volumes in youth at clinical high-risk for psychosis. Schizophr. Res. 213, 48–55.

Magalhães, R., Barrière, D.A., Novais, A., Marques, F., Marques, P., Cerqueira, J.,

Jay, T.M., 2018. The dynamics of stress: a longitudinal MRI study of rat brain structure and connectome. Mol. Psychiatry 23 (10), 1998.
McCutcheon, R.A., Bloomfield, M.A., Dahoun, T., Mehta, M., Howes, O.D., 2019. Chronic psychosocial stressors are associated with alterations in salience processing and corticostriatal connectivity. Schizophr. Res. 213, 56–64.
Mistry, S., Harrison, J.R., Smith, D.J., Escott-Price, V., Zammit, S., 2018. The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: systematic review. Schizophr. Res. 197, 2–8.
Pruessner, M., Cullen, A.E., Aas, M., Walker, E.F., 2017. The neural diathesis-stress model of schizophrenia revisited: an update on recent findings considering illness stage and neurobiological and methodological complexities. Neurosci. Biobehav. Rev. 73, 191–218.
Saunders, T.S., Mondelli, V., Cullen, A.E., 2019. Pituitary volume in individuals at elevated risk for psychosis: a systematic review and meta-analysis. Schizophr. Res. 213, 23–31.
Schifani, C., Hafizi, S., Tseng, H.H., Gerritsen, C., Kenk, M., Wilson, A.A., Mizrahi, R., 2019. Preliminary data indicating a connection between stress-induced prefrontal dopamine release and hippocampal TSPO expression in the psychosis spectrum. Schizophr. Res. 213, 80–86.
Subramaniam, A., LoPilato, A., Walker, E.F., 2019. Psychotropic medication effects on cortisol: implications for research and mechanisms of drug action. Schizophr. Res. 213, 6–14.
Tseng, H.H., Watts, J.J., Kiang, M., Suridjan, I., Wilson, A.A., Houle, S., Mizrahi, R., 2017. Nigral stress-induced dopamine release in clinical high risk and antipsychotic-naïve schizophrenia. Schizophr. Bull. 44 (3), 542–551.
Vaessen, T., Viechtbauer, W., van der Steen, Y., Gayer-Anderson, C., Kempton, M.J., Valmaggia, L., …, Morgan, C., 2019. Recovery from daily-life stressors in early and chronic psychosis. Schizophr. Res. 213, 32–39.
Vargas, T., Damme, K.S., Mittal, V.A., 2019. Bullying victimization in typically developing and clinical high risk (CHR) adolescents: a multimodal imaging study. Schizophr. Res. 213, 40–47.
Walker, E.F., Diforio, D., 1997. Schizophrenia: a neural diathesis-stress model. Psychol. Rev. 104 (4), 667.
Walker, E., Mittal, V., Tessner, K., 2008. Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. Annu. Rev. Clin. Psychol. 4, 189–216.
Zubin, J., Spring, B., 1977. Vulnerability: a new view of schizophrenia. J. Abnorm. Psychol. 86 (2), 103.