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Review

Social Stress and Psychosis Risk: Common Neurochemical Substrates?

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Environmental risk factors have been implicated in the etiology of psychotic disorders, with growing evidence showing the adverse effects of migration, social marginalization, urbanicity, childhood trauma, social defeat, and other adverse experiences on mental health in vulnerable populations. Collectively, social stress may be one mechanism that could link these environmental risk factors. The exact mechanism(s) by which social stress can affect brain function, and in particular the molecular targets involved in psychosis (such as the dopaminergic (DA) system), is (are) not fully understood. In this review, we will discuss the interplay between social environmental risk factors and molecular changes in the human brain; in particular, we will highlight the impact of social stress on three specific neurochemical systems: DA, neuroinflammation/immune, and endocannabinoid (eCB) signaling. We have chosen the latter two molecular pathways based on emerging evidence linking schizophrenia to altered neuroinflammatory processes and cannabis use. We further identify key developmental periods in which social stress interacts with these pathways, suggesting window(s) of opportunities for novel interventions. Taken together, we suggest that they may have a key role in the pathogenesis and disease progression, possibly provide novel treatment options for schizophrenia, and perhaps even prevent it.

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Psychosis is characterized by a constellation of symptoms that includes abnormal perceptions and beliefs, usually called positive symptoms. Negative symptoms (eg, anhedonia, social withdrawal, etc) and cognitive deficits (eg, impaired memory, attention, executive functions, etc) are also evident, and represent major predictors of functional outcome. Epidemiological data have consistently demonstrated a well-replicated association between early environmental social risk factors and psychosis. The exact mechanism(s) by which social stress can affect brain function, and in particular the molecular targets involved in psychosis (such as the dopaminergic (DA) system), are not fully understood. In this review, we will discuss the interplay between social environmental risk factors and molecular changes in the human brain; in particular, we will highlight the impact of social stress on three specific neurochemical systems: DA, neuroinflammation/immune, and endocannabinoid (eCB) signaling. We have chosen the latter two molecular pathways based on emerging evidence linking schizophrenia to altered neuroinflammatory processes (Carter *et al*, 2014) and cannabis use (Andreasson *et al*, 1987; Arseneault *et al*, 2002; Harley *et al*, 2010; Leweke *et al*, 2007; Morgan *et al*, 2013). Although a number of other neurochemical systems have been implicated in schizophrenia, such as the glutamate system (Carter *et al*, 2014; Coyle, 2012; Javitt, 2012), the scope of this review is limited to the molecular systems with existing human data on the effects of psychosocial stress, notwithstanding encouraging findings regarding stress-induced glutamate alterations obtained in animal studies (Gan *et al*, 2014; Jiang *et al*, 2013). In this article, stress is broadly defined as either cortisol alterations or social manipulations, which are appraised to exceed the adaptive capacity to cope.

EVIDENCE FOR THE ASSOCIATION BETWEEN SOCIAL STRESS, THE HYPOTHALAMUS–PITUITARY–ADRENAL AXIS, AND PSYCHOSIS

The etiology of schizophrenia is multifactorial and felt to reflect an interaction between genetic vulnerability and environmental contributors (Figure 1). Risk and protective factors, acting at a number of levels over time, appear to influence an individual's potential for developing of psychosis. In prospective longitudinal studies, it has been observed that individuals with schizophrenia experience an increased number of stressful life events in the period immediately preceding a relapse (Nuechterlein *et al*, 1992; Pallanti *et al*, 1997). This association is not entirely

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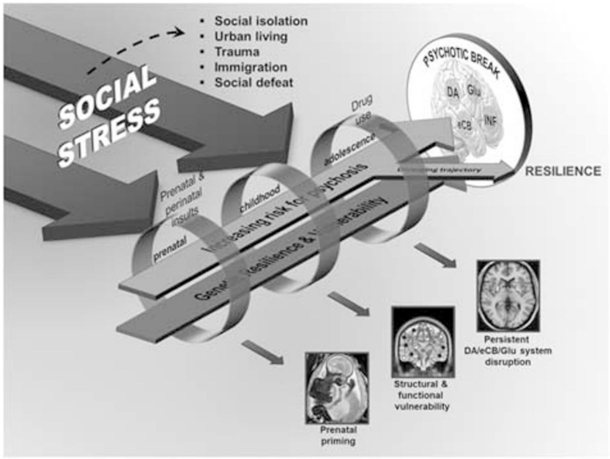

Figure 1 We have focused our review on three main neurochemical systems involved in psychosis: the dopaminergic (DA), endocannabinoid (eCB), and neuroinflammatory systems. However, the prominent role of the glutamatergic (Glu) system in psychosis cannot be ignored. Stage-specific stressors are indicated above the rings, whereas the big arrows represent the critical effect of social stress across all stages. The rings indicate possible environmental factors at each developmental stage that increase the risk for psychosis. At the early developmental stage, genetic vulnerability may combine with prenatal and perinatal insults (eg, maternal immune activation) to prime some individuals. In addition, social stressors experienced in childhood may lead to structural and functional development abnormalities leading to enhanced vulnerability, perhaps through environmental impact on gene expression (epigenetics). At the adolescence stage, in addition to the important social stressors typical for this age range (moving out of parental home, new schooling, peers), drug use affecting DA, Glu, and eCB signaling may amplify the premorbid neurochemical aberrancies carried over from prior stages. At all developmental stages, the genetic traits of the individual confer either resilience against or vulnerability leading to disease. A psychotic break occurs when multiple factors coalesce together, typically in early adulthood. Psychosocial or pharmacological interventions, addressing social stress and/or targeting these neurochemical systems in specific timings (such as in adolescence) may divert this trajectory away from psychosis towards resilience and health.

consistent (Hirsch *et al*, 1996), but gains further support from ecologically valid studies (ie, at the time of the event) (Myin-Germeys *et al*, 2005). Cortisol levels, an index of stress, have been positively associated with psychotic symptoms in schizophrenia (Walder *et al*, 2000), although results are not entirely consistent (Mondelli *et al*, 2010). Differences in the level of diurnal cortisol has been reported in schizophrenia (Mondelli *et al*, 2010; Walder *et al*, 2000). For example, higher levels of diurnal cortisol levels were reported in patients on antipsychotic treatments for <2 weeks as compared with controls or patients on antipsychotic treatments for >2 weeks (Mondelli *et al*, 2010). In addition, hypothalamus–pituitary–adrenal (HPA) over activity has been reported in schizophrenia patients including increased adrenocorticotropic hormone response to pharmacologic/psychosocial challenges (Elman *et al*, 1998) (for a review see Walker and Diforio, 1997) and abnormalities in glucocorticoid receptors (Perlman *et al*, 2004; Webster *et al*, 2002). A recent major multicenter study found that, after 2 years, high baseline cortisol levels predicted transition to psychotic level symptoms in at-risk youths (Walker *et al*, 2013). This is in line with a recent review, which suggests that, in conjunction with genetic risk factors, childhood adversity and trauma modifies the neurodevelopmental process resulting in increased stress sensitization during adolescence and early adulthood, leading to increased risk for psychosis (Howes and Murray, 2014).

Epidemiologic studies are consistent with the key role of stress/cortisol for psychosis. For example, the most consistent findings in the epidemiology of schizophrenia is the higher incidence of the disorder among migrant and ethnic minority groups (Akdeniz *et al*, 2014; Boydell *et al*, 2001; Morgan and Fearon, 2007; van Os *et al*, 2001). The reasons for the increased risk of schizophrenia and other psychoses in migrant groups are not entirely clear, but among other reasons, different forms of social stress may be responsible. Urbanicity, social isolation, social defeat, disrupted familial environment in early childhood, language and cultural maladjustment, childhood abuse, and persistent experiences of victimization and discrimination in migrants are important potential factors for psychosis (Morgan and Fearon, 2007; Selten *et al*, 2007). Growing up in an urban environment is associated with an increased risk of developing psychosis (Krabbendam and van Os, 2005; van Os *et al*, 2001, 2004) and abnormal brain responses to stress in normal volunteers (Akdeniz *et al*, 2014; Lederbogen *et al*, 2011). The finding of increased likelihood of psychosis in migrants when they live in environments where they represent a minority also reflects the impact of perceived social stress (Boydell *et al*, 2001). Consistent with this view, social defeat has been postulated as the underlying mechanism linking psychosocial aversive events to risk for psychosis (Selten *et al*, 2013). In line with this, the ethnic minority status in immigrants is associated with increased cortisol levels (Squires *et al*, 2012), social defeat with internalized racism is associated with dysfunctional diurnal cortisol secretion (Tull *et al*, 2005), and differential stress-related brain responses in urban dwellers (Akdeniz *et al*, 2014; Lederbogen *et al*, 2011). Moreover, flatter and steeper changes in diurnal cortisol levels have been found in severely and moderately neglected/abused individuals, respectively (van der Vegt *et al*, 2009). Furthermore, pronounced reductions in hippocampal volume, a brain region that has a key role in the HPA, has been repeatedly involved in psychosis (Wright *et al*, 2000).

PSYCHOSOCIAL STRESS AND DA SIGNALING

The predominant biological theory of schizophrenia holds that DA hyperactivity in the striatum (eg, associative striatum) represents a neurochemical abnormality underlying positive psychotic symptoms in schizophrenia (Howes and Kapur, 2009; Laruelle and Abi-Dargham, 1999). In line with this, the diathesis-stress model suggests that the HPA axis may trigger a cascade of events resulting in neural circuit dysfunction, including alterations in DA signaling (Walker and Diforio, 1997).

Positron emission tomography (PET) allows to investigate central DA response to stress in living humans. To date, a number of PET studies have shown increased DA release following either a psychosocial or a metabolic stress task (Adler *et al*, 2000; Pruessner *et al*, 2004). Pruessner *et al* (2004) was the first to report increased DA release in response to a psychosocial stress task in those who reported low maternal care. Reduction in [^{11}C]raclopride (a D2 antagonist radioligand) binding potentials in the ventral striatum relative to the non-displaceable compartment in the brain (BP_{ND}) during stress averaged ~10% (Pruessner *et al*, 2004), a magnitude of change of the same order as that observed after administration of amphetamine in healthy volunteers (Laruelle and Abi-Dargham, 1999). Interestingly, the amount of DA released, indexed as a reduction of [^{11}C]raclopride binding (BP_{ND}), was proportional to the salivary cortisol response to stress (Pruessner *et al*, 2004). The high correlation between the two values suggests a close link between cortisol and DA stress responses. This association was also replicated in a recent study using [^{11}C]-(+)-PHNO, a DA D2/3-specific agonist radioligand (Mizrahi *et al*, 2012). Adler *et al* (2000) has also provided further evidence, reporting that a metabolic stressor was linked to a significant reduction in striatal [^{11}C] raclopride BP_{ND}. However, changes in DA release were not replicated in a single study, which used a different stress paradigm, with no apparent social feedback (Montgomery *et al*, 2006). Although this line of research is important as it links task-related changes to alterations in DA receptor binding, it does introduce the potential confound of additional head movement.

Only one study investigated DA release in response to a psychosocial stress challenge in psychosis-related disorders. More specifically, Mizrahi *et al* (2012) showed significant displacement of [^{11}C]-(+)-PHNO in antipsychotic-naive patients with schizophrenia, with no effect in healthy volunteers; interestingly, an intermediate response was observed in those at elevated clinical risk for developing schizophrenia. Consistent with the PET data, the largest stress-induced changes in salivary cortisol was present in the schizophrenia group, followed by the clinical high-risk group (Mizrahi *et al*, 2012). Furthermore, the percent change in the cortisol response between the control and stress challenge was significantly associated with stress-induced DA release in the associative striatum (Mizrahi *et al*, 2012). Although these data do not prove causation, they provide the first evidence of increased DA release in response to a psychosocial stress challenge in psychosis-related disorders. This line of thinking would be consistent with recent theories of how stress may be affecting DA signaling. For example, stress is known to damage the hippocampus (Mondelli *et al*, 2010, 2011), a brain region commonly reported to be altered in both post-mortem (Benes, 1999) and imaging studies (Nelson *et al*, 1998) in schizophrenia, which was also proposed to underlie the DA hyperactivity in a well-validated animal model of schizophrenia (Lodge and Grace, 2007). In addition, preclinical studies showed a stronger connection between neonatal hippocampal injuries and increased stress-associated dopamine release (Cabungcal *et al*, 2014; Heinz *et al*, 1999). In summary, abnormal DA sensitivity in response to stress may be one pathway through which the social world interacts with biology to confer a higher risk of schizophrenia.

OTHER MOLECULAR MECHANISMS UNDERLYING PSYCHOSOCIAL STRESS AS A RISK FACTOR FOR PSYCHOSIS

Immune System and Psychosis

It is increasingly recognized that other molecular mechanisms may contribute to schizophrenia, and its vulnerability. For example, several lines of evidence point to a role for neuroinflammation in the pathogenesis of schizophrenia. These were recently reviewed (Carter *et al*, 2014), and the findings can be summarized as follows: (a) abnormal immune activation and elevated maternal proinflammatory cytokines during pregnancy significantly linked to later development of schizophrenia in offspring; (b) elevated inflammatory proteins (eg, cytokines) in schizophrenia patients; (c) potential significant modulatory effects of antipsychotics on neuroinflammation; (d) role for anti-inflammatory agents in the treatment of schizophrenia, including its putative prodrome; (e) PET studies either detected increased neuroinflammation or in negative studies, suggesting a significant association with positive psychotic symptoms and duration of illness; (f) association between psychosis and antibodies to membrane receptors; and (g) genome-wide association studies demonstrating a significant role of major histocompatibility complex genes in schizophrenia, among other genes (Consortium SWGotPG, 2014; Stefansson *et al*, 2009). Taken together, these studies suggest a prominent role for neuroinflammation/immune activation in psychosis.

Psychosocial Stress and the Immune System

Different forms of social stress have been associated with inflammatory responses, although the nature of the stress (eg, acute vs chronic, social vs physical) significantly affects these interactions. The stress inflammation link has been very well characterized in previous reviews (Kiecolt-Glaser *et al*, 2002); however, there has been some newer studies that add to the growing interest between psychosis, stress, and neuroinflammation. For example, acute psychosocial stress elevates proinflammatory interleukins and cortisol in healthy volunteers (Yamakawa *et al*, 2009) in those who experience negative affect (Carroll *et al*, 2011), as well as individuals exposed to early life stress (Carpenter *et al*, 2010), whereas childhood maltreatment and being raised in a 'harsh family' environment (Miller and Chen, 2010) has been linked to heightened peripheral markers of inflammation (Danese *et al*, 2007, 2008; Dennison *et al*, 2012; Hepgul *et al*, 2012). Social hierarchy appears to have a role in how stressors are perceived. For example, individuals who place themselves lower on the social ladder or feel lonelier demonstrate larger peripheral interleukin responses (eg, IL-6, CRP) when confronted with a psychosocial stress task *vs* those who place themselves higher on the social ladder (Coelho *et al*, 2014; Jaremka *et al*, 2013). Unfortunately, as of yet no study has investigated the role of psychosocial stress on the immune response in patients with schizophrenia-related disorders.

In preclinical studies, stress (glucocorticoid administration) induces activation of inflammatory responses in activated microglia (Frank *et al*, 2010) and, conversely, inflammatory cytokines can disrupt glucocorticoid receptor function (Pace and Miller, 2009). For example, stress-induced alterations in the glucocorticoid receptor can disrupt the well-recognized ability of glucocorticoids to restrain the inflammatory response (Rhen and Cidlowski, 2005). In a recent study, prenatal immune activation and peripubertal stress produced synergistic effects in the development of key sensorimotor gating deficiencies such as prepulse inhibition and acoustic startle reflex, both considered viable (albeit deficient) animal models of schizophrenia. Later applications of stress (ie, not peripubertal but in adulthood) do not elicit these same alterations, underscoring the precise timing of the postnatal stress challenge vis-á-vis its interaction with the prenatal immune system. Taken together, prenatal immune activation and peripubertal stress lead to enhanced DA levels in the hippocampus, increased expression of markers of activated microglia in the hippocampus and prefrontal cortex, and elevated levels of proinflammatory cytokines (Giovanoli *et al*, 2013). In summary, neuroinflammation would thus appear to be another molecular pathway through which social stress can affect neurochemistry and alter brain function/structure in a manner that increases risk for schizophrenia.

Cannabinoids and Psychosis

Cannabinoids, the active components of cannabis, exert their effects on the brain by acting on the eCB system. The eCB comprises the enzymes involved in their synthesis (eg, diacylglycerol lipases) and inactivation (eg, fatty acid amide hydrolase (FAAH); monoacylglycerol lipase), as well as the receptors (eg, CB1, CB2) that mediate physiological effects of the eCBs (anandamide (AEA) and 2-arachidonoyl-glycerol) (Di Marzo *et al*, 1994). Among other functions, the eCB system is involved in neuroprotection, modulation of nociception, control of certain phases of memory processing, modulation of immune and inflammatory responses, and appetite regulation (Di Marzo *et al*, 1994). eCB synaptic signaling works in a retrograde manner (Wang and Ueda, 2009).The lipophilic eCBs, including AEA and 2AG, are synthesized 'on demand' in the postsynaptic neuron and released into the synapse without any vesicular storage (Wang and Ueda, 2009). These molecules then bind to G-protein-coupled CB1 receptors in the presynaptic neuron (Kreitzer and Regehr, 2002) to modulate neurotransmitter release.

Over the years, a number of separate lines of research have converged on cannabinoids, including eCBs, as key contributors to schizophrenia: (a) ~2-fold increase in the incidence of schizophrenia with early cannabis use (Andreasson *et al*, 1987); (b) elevated levels of eCBs in cerebrospinal fluid (CSF) of patients with schizophrenia, including marked (up to eightfold) elevations of AEA (Leweke *et al*, 2007); (c) reduced peripheral expression of eCB synthesis enzymes and increased expression of degradative enzymes in first episode schizophrenia (Bioque *et al*, 2013); (d) potential association between CB1 receptors polymorphism (CNR1) and schizophrenia (Ujike *et al*, 2002); (e) increased CB1 binding in the dorsolateral prefrontal cortex (Jenko *et al*, 2012) and anterior cingulate cortex based on post-mortem autoradiography studies (Zavitsanou *et al*, 2004); and (e) elevated CB1 binding *in vivo* in patients with schizophrenia, as measured by two PET studies (Ceccarini *et al*, 2013; Wong *et al*, 2010). Although still in its infancy, these studies sometimes, with inconsistent findings, point to a prominent role of eCB in schizophrenia.

Psychosocial Stress and eCB

The presence of CB1 receptors within the corticolimbic circuits regulating the HPA axis, in combination with the stress-reducing properties reported by cannabis users, suggests a role for the eCB system in stress regulation. Animal studies have provided compelling evidence implicating the eCBs and, in particular, AEA in the regulation of the HPA axis (Hill *et al*, 2005, 2009; Rademacher *et al*, 2008). For example, both acute and repeated restraint stress increase FAAH hydrolytic activity and decrease AEA (Hill *et al*, 2009, 2013; Rademacher *et al*, 2008). The main site providing excitatory drive to the HPA axis is the amygdala (Herman *et al*, 2005), which regulates the extent of HPA axis responses to stressful stimuli (Hill *et al*, 2009). Tonic AEA release from the amygdala activates CB1 receptors, which decreases glutamate release and ultimately dampens excitatory afferents to the amygdala (Hill *et al*, 2009) and disinhibits it. These studies suggest that the eCB system is well implicated in the stress response. At a functional level, there is growing interest in the putative interactions between the HPA and eCBs. More specifically, it has been suggested that glucocorticoids recruit eCB in the amygdala to consolidate and store memory (Atsak *et al*, 2012; Campolongo *et al*, 2009). In addition to contributing to the adaptation of the HPA axis to stressful stimuli, eCB signaling in the amygdala also appears to be important in behavioral adaptation to aversive stimuli. For example, mice lacking the CB1 receptor exhibit prolonged expression of fear behaviors (Marsicano *et al*, 2002). This suggests that the eCB signaling system is an important safeguard against the effects of stress and the physiological aspects of the stress response. Interestingly, cannabinoids elicit behavioral as well as neurochemical changes that are dependent on the environmental conditions under which they are administered. For example, Δ9-tetrahydrocannabinol (THC) administered to rats housed in stressful conditions increase striatal DA uptake and metabolism, whereas such an effect is absent in rats housed under normal conditions (Littleton *et al*, 1976; MacLean and Littleton, 1977). Further to this point, cross-sensitization between THC and stress has been reported (Suplita *et al*, 2008), suggesting that the physiological and psychological effects of cannabis may be altered in individuals experiencing environmental adversity. We recently investigated potential cross-sensitization between stress and cannabis in those at risk of developing schizophrenia, showing an absence of increased DA release in response to a psychosocial stress task despite increased positive attenuated psychotic symptoms (Mizrahi *et al*, 2014). Such results are in line with studies involving patients with schizophrenia and concurrent substance use (Thompson *et al*, 2013), as well as cannabis users with psychotic experiences (Bloomfield *et al*, 2014), and suggest that even minute increases in DA release lead to increased psychotic-like experiences in these populations. A potential explanation comes from animal studies showing postsynaptic supersensitive DA D2 receptors in conjunction with drug use (Ginovart *et al*, 2012). Substance abuse frequently begins before the first psychiatric episode in schizophrenia (Hafner *et al*, 2013). Hafner *et al* (2013) demonstrated that cannabis abuse reduced the mean age of schizophrenia onset (17.7 years) as compared with patients without misuse (25.7 years). Patients with schizophrenia and those at risk for the illness exhibit alarmingly high levels of drug use, most commonly cannabis (Fowler *et al*, 1998; Regier *et al*, 1990), despite increased risk of psychotic experiences. This may be due to the incentive sensitization theory of addiction where continued drug consumption may cause a drug-induced increased DA sensitivity (Heinz, 2002; Robinson and Berridge, 1993). Of note, risk of psychosis has been shown to increase with childhood trauma and cannabis use through a synergistic interaction (Harley *et al*, 2010). Both chronic drug use and chronic stress can disrupt the eCB system leading to an impaired response to stress (Popoli *et al*, 2011). It is conceivable that social stress in vulnerable individuals leads to a dampened eCB system, further increasing cannabis use to potentially regulate the abnormal stress response; in turn, stimulation of CB1 receptors by exogenous cannabis may suppress the HPA response to stress (Mizrahi *et al*, 2014), thereby providing an ‘external buffer’. However, further studies are needed to understand the role of cannabis use on HPA axis and its relevance for psychosis and psychosis risk.

Although this hypothesis may be a reasonable explanation for the observed elevated cannabis use in those at risk and in patients with psychosis, it does not explain why cannabis use itself may lead to psychosis in at-risk populations. There is no data as of yet to answer this question. In fact, our understanding of eCB in psychosis and in cannabis users is very limited. While high AEA levels have been reported in the CSF of patients with schizophrenia and putative prodromal states, these are negatively associated with psychotic symptoms. In those at risk for psychosis, those with low AEA levels were more likely to transition earlier to psychosis (Koethe *et al*, 2009). Further, heavy cannabis use was associated with lower CSF AEA and negatively correlated with (cannabis-free) psychotic symptoms (Morgan *et al*, 2013). No doubt that investigating the eCB in living human brain of patients with psychosis and psychosis risk with and without cannabis use is needed. Notably, the eCB system undergoes marked changes in early life and adolescence until early adulthood (Long *et al*, 2012). These early life changes could potentially explain the sensitivity of this age group to cannabis use and social stress on those vulnerable for schizophrenia. In line with this, it has been shown that early cannabis use (before 16 years old) leads to increased risk for psychosis (Arseneault *et al*, 2002), and animal studies suggest a critical effect in this particular time period (Cass *et al*, 2014). In this regard, understanding the role of the eCB system, particularly during adolescence, may provide novel targets for stress regulation in at-risk populations.

TOWARDS AN INTEGRATED VIEW OF EARLY MOLECULAR CHANGES OCCURRING DURING SOCIAL STRESS AND PSYCHOSIS RISK

Advances in our understanding of schizophrenia underscore both its complexity and heterogeneous nature. Given that the illness does not routinely declare itself until late adolescence/early adulthood, numerous influences may have a contributory role during this interval, reflected across presentation, symptomatology, illness trajectory, and response to treatment (Case *et al*, 2011).

In this regard, very little is known about how the DA system, eCB, and neuroinflammatory pathways affect clinical presentation, trajectory, and response to treatment. Although elevated DA response to amphetamine has been reliably associated with both positive psychotic symptoms and antipsychotic response (Abi-Dargham *et al*, 2009; Laruelle and Abi-Dargham, 1999), no clinical picture is defined following eCB or inflammatory markers alterations. It may well be that enhanced neuroinflammation in psychosis could be particularly relevant to cognitive and depressive and/or negative symptoms. Notably, neuroinflammation is proposed in the pathogenesis of major depression (for a review see Miller *et al*, 2009), and is associated with significant risk of suicide attempts (Bottlender *et al*, 2000; Harvey *et al*, 2008). Thus, indirect evidence suggests a possible role of neuroinflammation in depressive symptoms in psychosis. Only two studies examined the relationship between C-reactive protein and cognitive symptoms in schizophrenia and both found lower scores on Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Dickerson *et al*, 2007, 2012). In addition, increased S100B levels showed impaired performance on auditory verbal learning test in schizophrenia patients (Pedersen *et al*, 2008). Collectively, these data suggest a possible role of neuroinflammation in cognitive and depressive symptoms, and perhaps even priming the immune system for vulnerability to stress (Giovanoli *et al*, 2013).

The role of eCB in psychosis clinical picture, trajectory, and response to treatment is unclear, given the paucity of data in this regard. Although still in its infancy, eCB research has suggested that it is likely that the eCB will show a prominent role in stress regulation, a line of research that needs further investigation in CHR as well as first episode psychosis patients. Because the eCB system also has a critical role in the modulation of neurotransmitter release, including dopamine and glutamate via activation of the CB1 cannabinoid receptor (Prescot *et al*, 2013), it is well positioned in the central nervous system to exert presynaptic inhibition of synaptic transmission at both excitatory and inhibitory synapses (Harkany *et al*, 2008).

In this regard, the use of clinical presentation/brain changes rather than diagnostic groups (as suggested by the NIMH Research Domain Criteria (RDOC)) would prove to be more beneficial, such that each neurochemical alterations (DA, immune, and eCB) is tapped into a particular symptoms domain and/or cluster of brain structural/functional alterations. Explorations for correlations of neurochemical alterations with cognitive/behavioral symptoms provide the opportunity to uncover novel subgroups that feature prominent phenotypes reducing heterogeneity, likely increasing response to more specific treatments.

Furthermore, the potential joint alteration of these three systems has never been explored in patients with psychosis, except for the first report of Perkins *et al* (2015) reporting both immune and HPA axis dysregulation that jointly seem to predict psychosis transition. In summary, similar studies are needed where more than one system is interrogated. Although this will likely increase sample sizes and complexities in data analysis, multisite studies and collaborations among scientists may be able to bridge this gap. Finally, these three systems could be used to stratify participants for clinical trials, for psychosis conversion, and response to treatments. In the search for new treatment options, establishing reliable altered biomarkers represents an important step in facilitating the evaluation of new molecular compounds. Finally, because interventions, pharmacological and/or psychosocial, seem exquisitely sensitive to time (ie, in adolescence *vs* adulthood), future studies should as well emphasize carefully selected populations that address both age and social environment.

Research of this sort faces considerable challenges. Imaging approaches appropriate for investigating these novel neurochemical systems in humans *in vivo* are in the early stage of development, with specific PET radioligands that target microglial activation/neuroinflammation and eCB only becoming available recently (Damont *et al*, 2013; Horti *et al*, 2006). Furthermore, these three systems are sensitive to multiple environmental perturbations, including social stress and drug use, making measurements in clinical populations a challenge. The complexity of the temporal aspect of the progression towards disease and capturing the ‘critical window’, with some biomarkers putatively not appearing until very late in the course to disease, whereas others potentially being present from very early (ie, childhood) may also hinder potential novel interventions. Additionally, the DA, eCB, and inflammatory pathways addressed in this review are not the only molecular aspects of psychosis. Finally, new data demonstrate the complex interplay of these systems (Katona and Freund, 2008), making it difficult to tease apart the independent contributions of each in clinical studies. This could, although, also be seen as an advantage in that close links between these systems suggest the possibility to target one, whereas at the same time influencing the other. For example, cannabidiol, a major component of cannabis, has been reported to have an antipsychotic effect (Leweke *et al*, 2012). Whether this is due to its potential anti-inflammatory properties (Carrier *et al*, 2006) or its putative FAAH blockage role is currently unknown (Robson *et al*, 2014). Nevertheless, it provides an example of a compound that could target more than one system at the same time. Furthermore, preclinical studies that elucidate the role of social stress on these molecular pathways, and their interactions including causation/directionality would become key to truly understand these complexities.

Currently, the most widely available treatment for schizophrenia is antipsychotic medication: compounds developed for their effects on neurotransmitters, in particular dopamine. Cognitive behavioral trials have shown provocative findings in those at elevated risk for psychosis (Stafford *et al*, 2013), but space remains to investigate the potential effects of these and other novel psychosocial interventions targeting social stress. Based on the evidence detailed here, eCB signaling and neuroinflammation may well represent valuable new targets for drug development, notwithstanding the aforementioned challenges. Within a framework that incorporates these novel neurochemical processes, opportunities arise for non-pharmacological strategies to address the significant impact of social stress. Focusing on adolescents with multiple risk factors as a starting point, social programs addressing empowerment and resilience, drug use treatment, immigrants’ supports to reduce discrimination and marginalization, cognitive training, and so on could impact the way schizophrenia is managed within the society. Investigating how these potential factors affect molecular targets in brain may provide novel ways to treat schizophrenia, perhaps even preventing it.

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