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Chronic stress, structural exposures and neurobiological mechanisms: A stimulation, discrepancy and deprivation model of psychosis

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Abstract

Chronic stress exposure has been established as a key vulnerability factor for developing psychotic disorders, including schizophrenia. A structural, or systems level perspective, has often been lacking in conceptualizations of chronic stress for psychotic disorders. The current review thus identified three subtypes of structural exposures. *Stimulation* exposures included urban environments, population density and crime exposure, with intermediary mechanisms of lack of safety and high attentional demands. Underlying neural mechanisms included threat neural circuits. *Discrepancy* exposures included environmental ethnic density, income inequality, and social fragmentation, with intermediary mechanisms of lack of belonging and social exclusion, and neural mechanisms including the oxytocin system. *Deprivation* exposures included environments lacking socioeconomic, educational, or material resources, with intermediary mechanisms of lack of needed environmental enrichment, and underlying neural mechanisms of over-pruning and protracted PFC development. Delineating stressor etiology at the systems level is a necessary step in reducing barriers to effective interventions and health policy.

1. Introduction

Psychotic disorders, including schizophrenia, are chronic and highly debilitating, estimated as one of the top 15 leading causes of disability worldwide (Vos et al., 2017). Psychotic disorders are characterized by marked decreases in cognitive, social and role functioning, accompanied by symptoms such as delusions, hallucinations, and disorganized communication. Risk factors for developing a psychotic disorder include genetic and biological pre-existing vulnerabilities, as well as chronic stress exposure, which can over time exacerbate pre-existing vulnerabilities and drive illness onset. Thus, chronic stress exposure has long been implicated as a central etiological factor in the development of psychotic disorders. Through animal and human models, decades of insightful research have yielded a strong understanding of the underlying neurobiological systems implicated in the effects of chronic stress exposure. Simultaneously, the literature is rich with regards to measuring specific individual level stressors, including exposure to bullying, school performance stress, parental instability, among other life events. As individuals we exist within a larger environmental and social context (i.e., structural level factors) which, if

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harmful, may confer chronic stress at the systems level (Bronfenbrenner, 1994; Glass & McAtee, 2006). Certain local or even country level structural characteristics (such as neighborhood socioeconomic status and crime exposure) may systemically affect the health and well-being of the individuals inhabiting these environments, instituting barriers to healthy living and development. Since these structural impacts are not captured when exclusively considering individual level stressors, it then becomes necessary to more thoroughly incorporate structural level stressors when considering models for risk of developing psychopathology.

The psychosis literature has widely begun to explore structural characteristics, and found compelling evidence of associations of certain structural characteristics with psychotic disorder incidence. Given the literature, one can deduce that exposure to adverse structural level factors engages converging mechanisms that underlie the harmful effects of stress on physical and mental health. Nonetheless, it is critical to consider that stressors with phenomenologically differing components may also impact neural function and neurodevelopment in distinct manners. The research on neural effects of different stressors is well developed; however, to our knowledge there have been no attempts to synthesize the literature on structural stressors and psychosis risk with the research on distinct neurobiological effects of certain stressors. Further understanding the mechanistic neural effects of different structural exposures is essential from an epidemiological and etiological standpoint. Increasing our understanding of structural barriers to mental health stands to inform health policy, as well as prevention and intervention efforts at the societal level. Thus, in the current review, we first aim to discuss converging biological mechanisms of chronic stress exposure, which are theoretically impacted by structural stressors broadly defined. We then will propose three kinds of structural environmental exposure. Relations between the three exposures and risk for developing psychosis will be discussed in the context of a *stimulation*, *discrepancy* and *deprivation* model of chronic stress in psychosis, along with possible intermediary mechanisms and neurobiological underpinnings of these associations. Before we can discuss converging biological mechanisms of chronic stress exposure, along with the three areas and subsequent conceptual model, it is first necessary to discuss certain caveats that are central to any discussion of these subjects.

1.1 Co-occurrence and convergence of structural exposures

The review aims to differentiate three types of structural stressors: stimulation, *deprivation*, and *discrepancy*. *Stimulation* includes environments that activate threat neural systems and confer feelings of lack of safety and an excess of sensory inputs/attentional demands. *Deprivation* describes environments that have a lack of necessary stimuli for brain health and normative maturation. *Discrepancy* describes environments that foster a sense of social exclusion, isolation, or lack of belonging. Before describing these in more detail, it is crucial to acknowledge caveats related to overlap in exposures. Far from being isolated exposures, there is reason to believe the structural stressors that will be discussed co-occur rather frequently. For example, it is intuitive to imagine *stimulation* exposures such as high crime environments very often co-occurring with *deprivation* exposures such as low neighborhood socioeconomic status. Therefore, we do not seek to hypothesize that these exposures occur independently of each other. Rather, the review seeks to highlight the evidence that these

exposures each individually effect risk for developing a psychotic disorder. As will be discussed in more detail below, the literature has often controlled for exposure to co-occurring structural factors, and found this not to alter associations with increased psychosis risk for each of the three structural exposures discussed below. Similarly, with regards to neural and intermediary mechanisms underlying each exposure, while the review seeks to differentiate between neural systems that could be affected by each specific exposure, it is also critical to acknowledge neural systems that could be affected through chronic stress exposure by all structural stressor types. The review poses that while converging neural effects exist, the impact of specific structural stressor types can be measured independently, and confer unique effects on neural function, which are valuable to understand and further explore.

1.2 Social drift

When discussing structural exposures, it is necessary to consider possible effects due to what is defined as “social drift.” That is, vulnerable individuals may tend toward moving into more adverse neighborhood environments as emerging symptoms interfere with access to resources and day to day functioning. However, there is evidence that the effects of *stimulation* (March et al., 2008; Tandon, Nasrallah, & Keshavan, 2009), *discrepancy* (Termorshuizen, Smeets, Braam, & Veling, 2014), and *deprivation* exposures (Kirkbride, Jones, Ullrich, & Coid, 2012) on increased incidence of psychotic disorders remain even after accounting for social drift. Thus, while social drift may certainly be an influence in some cases, it is notable that many of the studies discussed in this review have accounted for social drift in their methods and study conceptualizations.

2. Converging mechanisms impacted by the three structural exposures

Chronic exposure to structural adverse environmental conditions, (whether these occur pre-natally, during early-postnatal periods, childhood, or adolescence through young adulthood) is likely to confer chronic stress, resulting in hypothalamic-pituitary-adrenal (HPA) dysregulation, a key factor in diathesis-stress conceptualizations of psychosis (Pruessner, Cullen, Aas, & Walker, 2017). Chronic stress is also causally linked to aberrant dopamine and glutamate transmission; this association is etiologically compelling, as dopamine dysregulation is closely linked with positive symptoms, and glutamate transmission has been associated with negative symptoms and cognitive dysfunction (Grace, 2016; Howes, McCutcheon, & Stone, 2015; Pruessner et al., 2017). Chronic inflammation resulting from chronic stress exposure is another putative mechanism conferring psychosis risk (Bergink, Gibney, & Drexhage, 2014). Dysregulation in these systems is liable to impact the brain in complex and multifaceted manners, which will be briefly delineated below.

2.1 HPA dysregulation

Chronic stress-induced prolonged HPA axis activation, leading to hyper secretion of glucocorticoids, can have detrimental effects on neural structure and function. Importantly, normative increases in cortisol secretion in adolescence and early adulthood coincide with the typical period of onset for psychotic disorders. With regards to the HPA axis, there is strong evidence that dysregulation due to chronic stress exposure could impact the prefrontal

cortex (PFC) and hippocampus most prominently (Grace, 2016; Howes et al., 2015; Mittal & Walker, 2019; Pruessner et al., 2017; Walker, Mittal, & Tessner, 2008).

2.2 Dopamine dysregulation

Dopamine sensitization is both sensitive to chronic stress exposure broadly defined, and intricately related to psychotic disorder etiology. Chronic stress exposure leads to increased activity of dopamine neurons across the ventral tegmental area (VTA), PFC and nucleus accumbens (Grace, 2016). Grace and colleagues pose a key mechanism for downstream dopamine dysregulation involves interneurons, which enable brain information transfer and system coherence. Given that interneurons are among the last components to be incorporated during neurodevelopment, they are particularly susceptible to harm due to oxidative stress, most markedly early in the post-natal period. Thus, multiple hits beginning early in post-natal development and occurring additionally through adolescence and young adulthood (coinciding with normative increases in cortisol secretion) may lead to compounded interneuron loss during multiple critical periods, which would then confer increased risk of chronic dopamine dysregulation, and of development of psychotic disorders as a result. For instance, it seems that chronic stressors activate the dopamine system by acting on the hippocampus, which is also observed to be widely dysregulated in psychotic disorders; importantly, anterior hippocampus hyperactivity has been found to correlate both with presence of psychosis and with substantial decrease in interneurons in the hippocampus.

2.3 Glutamate dysregulation

Though the literature has been less prolific on the subject, studies have shown associations between chronic stress exposure and glutamate transmission, including glutamate release, receptors, clearance and metabolism (Popoli, Yan, McEwen, & Sanacora, 2012). In addition, abnormalities in hippocampal glutamatergic neurotransmission may be associated with elevated striatal dopamine, which could increase risk for developing a psychotic disorder (Howes et al., 2015; Stone et al., 2010).

2.4 Inflammation

Lastly, chronic inflammation resulting from chronic stress exposure has also been recently hypothesized as a mechanism through which chronic stress could confer increased risk for psychotic disorders (Bergink et al., 2014). Peripheral inflammation resulting from chronic early life and current structural stress exposure could lead to neuroinflammatory responses impacting cortico-amygdala function, as well as PFC structure, function and development (Nusslock & Miller, 2016).

2.5 Stimulation discrepancy deprivation model of psychosis

In the next sessions, the different types of structural exposures comprising the *Stimulation Discrepancy Deprivation* (SDD) model of psychosis will be described in detail (Fig. 1). The sections will include discussion of influences on different neural systems, as well as intermediary mechanisms through which these exposures could impact brain function and development.

3. Stimulation structural exposure

3.1 Stimulation definition and relations to psychotic disorder risk

The first dimension is defined as “*stimulation*” neighborhood environments. Neighborhood environments in this dimension include urban/rural classifications, population density, and exposure to crime. Living in an urban environment has long been established as a risk factor for developing psychotic disorders (Kelly et al., 2010; Krabbendam & Van Os, 2005; March et al., 2008; Takei, Sham, O’Callaghan, Glover, & Murray, 1995; Vassos, Pedersen, Murray, Collier, & Lewis, 2012). There is evidence that the robustly observed effect applies across the continuum of rural to urban. Increasing levels of rurality have been associated with reduced risk for affective psychosis (Omer et al., 2016). Further, meta-analytic evidence suggests a linear relationship between increasing urbanicity and odds of risk for schizophrenia (Vassos et al., 2012), consistent with previous findings of a dose-response relationship (Pedersen & Mortensen, 2001). The association between urbanicity and psychotic experiences holds across the psychosis spectrum, and remains after accounting for confounds such as family socioeconomic status, family psychiatric history, and substance use problems (Newbury et al., 2017). Experimental paradigms of busy urban environments have found urban “street exposure” results in significant increases in psychotic symptoms (Freeman et al., 2014). Relatedly, high population density, which characterizes urban areas, has been similarly associated with increased psychosis risk (Kirkbride et al., 2012). Emerging literature has also considered crime exposure and victimization as an additional exacerbating factor for increasing psychosis risk. For example, it has been found that adverse neighborhood social conditions and personal crime victimization combined exhibit a stronger association with psychotic experiences than either exposure alone (Newbury et al., 2017). Within urban areas specifically, associations have been found between high crime levels and incidence of schizophrenia (Bhavsar, Boydell, Murray, & Power, 2014).

3.2 Stimulation intermediary mechanisms

Structural exposures of urban environment, high population density, and high crime exposure share features through which they could negatively impact the individual and increase vulnerability for mental illness. The urban environment for one is often characterized by features such as significantly heightened levels of population density, which could act as visual stressors, offering chronic high levels of stimuli/attentional demands in an individual’s environment (Gong, Palmer, Gallacher, Marsden, & Fone, 2016). In addition to population density, urban environments are also characterized by physical features such as limited “green” space, high noise levels, graffiti, increased rubbish, traffic, as well as hazardous waste sites (Weich et al., 2002). Taken together, these features could enact adaptation processes resulting in chronic heightened vigilance and physical arousal resulting from efforts to ensure safety and identify possible threats in the environment. Urban “street exposure” has indeed been linked in experimental paradigms to increased psychotic symptoms, as well as accompanying increases in paranoia and anxiety (Freeman et al., 2014). Epidemiologic and meta-analytic studies have also repeatedly observed associations between living in urban environments and increased psychological distress, along with risk for mental illness (including anxiety, depression, and psychosis) (Breslau, Marshall, Pincus, & Brown, 2014; Gong et al., 2016; Lederbogen et al., 2011; McKenzie,

Murray, & Booth, 2013; Wilson-Genderson & Pruchno, 2013). Another facet that often characterizes urban environments is greater average crime rates (Jones & Fanek, 1997). Greater exposure to crime in an urban environment could exacerbate heightened chronic physical arousal and vigilance, leading to feelings of threat and lack of safety. This notion that high-crime urban conditions can lend themselves to chronic heightened physical arousal and vigilance is supported by investigations finding that perceptions of neighborhood safety along with exposure to neighborhood violence are important predictors of symptoms in otherwise healthy individuals (Wilson-Genderson & Pruchno, 2013).

3.3 Stimulation exposure neural mechanisms

The discussed components of neighborhood environments that are urban, have high population density, or have high exposure to crime could make them liable to alteration of neural threat systems. Chronic exposure to environments that could evoke feelings of threat or lack of safety in turn could affect the structure, function, and connectivity of threat circuit regions including the amygdala, hippocampus, and ventromedial prefrontal cortex (vmPFC) (McLaughlin, Sheridan, & Lambert, 2014). The literature offers compelling evidence that chronic exposure to threatening stimuli, especially during key developmental periods, can adversely impact these neural circuitry underlying fear conditioning and extinction (McLaughlin, Sheridan, & Lambert, 2014). Functions of the amygdala include detection of salient environmental stimuli, along with processing of emotion related cues (LeDoux, 2003; Tottenham & Sheridan, 2010; van Marle, Hermans, Qin, & Fernández, 2009). There is evidence that the amygdala plays an essential role in threat detection and identification (Adolphs, 2008; Isenberg et al., 1999; Öhman, 2005), and it is also key for acquiring and expressing learned fear (Harnett et al., 2019; Johansen, Cain, Ostroff, & LeDoux, 2011; LeDoux, 2003). Chronic exposure to highly stimulating and populated urban environments thus may over time impact novel fear learning. Over time, this could result in hypervigilance, along with a lowered threshold for experiencing fear as an incremental number of neutral cues are flagged as threatening; eventually leading to abnormal amygdala function (Cohen et al., 2013; van Marle et al., 2009).

The vmPFC is also critically involved in both fear inhibition and retention of extinction learning (Phelps, Delgado, Nearing, & LeDoux, 2004; Quirk, Russo, Barron, & Lebron, 2000). Importantly, the vmPFC also has direct projections to and down-regulates the amygdala (Milad & Quirk, 2012; Milad et al., 2007; Quirk et al., 2000; Quirk, Likhtik, Pelletier, & Paré, 2003). For example, vmPFC activation during recall of extinction memory serves the role of inhibiting amygdala activity, thus dampening fear expression and facilitating extinction of learned feared stimuli (Knapska & Maren, 2009; Milad & Quirk, 2002). Another region that is implicated is the hippocampus. Early chronic threat exposure could impact hippocampal function and morphology through triggering shortening of dendritic spines and arborization (Brunson, Eghbal-Ahmadi, Bender, Chen, & Baram, 2001; Ivy et al., 2010). Early threat exposure has been shown to impact hippocampus-dependent facets of fear conditioning in animal models (Ishikawa et al., 2012; Matsumoto et al., 2008). Impairments in synaptic transmission within the vmPFC-hippocampus circuit have also been observed to result from impairments in fear extinction following prolonged early threat exposure (Toledo-Rodriguez & Sandi, 2007). Studies directly tying the structural exposures

of urbanicity, population density and exposure to crime to threat neural circuitry have been scarce. Nonetheless, there is some evidence supporting these theories with regards to exposure to community violence. For example, a recent investigation of adolescents found an association between community violence exposure and lower hippocampal and amygdala volumes, as well as altered frontolimbic connectivity (Saxbe et al., 2018).

With regards to neural correlates of structural exposures in this domain, there is also robust evidence for the dorsolateral prefrontal cortex (dlPFC) and ACC being impacted by exposure to threat. For example, the lateral prefrontal cortex and ACC have both been shown to be implicated in processing of threat related stimuli (Bishop, Duncan, Brett, & Lawrence, 2004). The dlPFC specifically has also been shown to play a role in processing novel vs older stimuli while undergoing threat experiences (Balderston, Hsiung, Ernst, & Grillon, 2017). There is compelling evidence that living in urban regions may impact these threat circuitries. For instance, increased amygdala activity has been found in those living in urban regions, and activity in the perigenual anterior cingulate cortex (ACC), which regulates the amygdala, has been linked to urban upbringing (Lederbogen et al., 2011). Consistent with this finding, another investigation found urban upbringing related to lowered volumes in the right dlPFC and perigenual ACC (Haddad et al., 2014). Taken together, the existing literature allows for educated theorizing with regards to the specific effects of the urban/population density/crime exposure dimension. Future studies will benefit from enriching our understanding of this subject through linking specific structural exposures to neural mechanisms more directly.

4. Discrepancy structural exposure

4.1 Discrepancy definition and relations to psychotic disorder risk

The “*discrepancy*” dimension comprises neighborhood conditions including inequality, ethnic density, and high social fragmentation. Income inequality constitutes variation in income distributions within neighborhoods. High income inequality comprises great *discrepancy*, or heterogeneity, in incomes within a neighborhood, with low income inequality conversely meaning the neighborhood income distribution is relatively homogeneous. Studies have found an association between psychosis incidence and higher levels of income inequality. One investigation of 56 neighborhoods in London found that even after controlling for individual level factors and standardizing for age, sex ethnicity and socioeconomic status, greater income inequality explained substantial variation in psychosis risk (Kirkbride et al., 2012). Another investigation spanning 26 countries found a relationship between income inequality (assessed by the Gini index) and incidence of schizophrenia. Here also, the association between income inequality and schizophrenia incidence was not accounted for by urbanization, migration status, unemployment rate, population density, or gross domestic product per capita (Burns, Tomita, & Kapadia, 2014).

Also comprising part of the “*discrepancy*” dimension, ethnic density is defined as proportion of individuals in one’s neighborhood that have a similar ethnic background. Higher ethnic density would entail more individuals in one’s neighborhood that share a similar ethnic background. On the other hand, low ethnic density denotes a neighborhood in which there is a low proportion of individuals that share a similar ethnic background. Research has found

living in lower ethnic density neighborhoods relates to increased incidence of psychosis in immigrant groups (Schofield et al., 2017; Veling et al., 2008). Compared to the general population, elevated rates of psychotic disorders have been consistently observed among ethnic minorities more generally (Lasalvia et al., 2014; Termorshuizen et al., 2014). This effect may be lessened, however, in areas with high ethnic density (Schofield et al., 2017; Termorshuizen et al., 2014; Veling et al., 2008).

Lastly, social fragmentation factors into the “*discrepancy*” dimension. Social fragmentation and its counter, social cohesion, are characterized by the stability and structure of a given social environmental context. Social fragmentation can be operationalized through proportion of rental housing, frequency of changes in living arrangements among residents of a certain neighborhood (i.e., population turnover), proportion of single and/or divorced individuals in a neighborhood, as well as neighborhood disorder. High social cohesion, on the other hand, can be measured by aspects such as whether neighbors have shared values, trust each other, or are able to develop stable relationships within the neighborhood context (Crush, Arseneault, Jaffee, Danese, & Fisher, 2017). Research suggests that indexing social fragmentation distinctly from urban status and *deprivation* could be valuable. For example, studies found areas characterized by high social fragmentation had higher admission rates for psychosis, even after accounting for both *deprivation* and urban/rural living status (Allardyce et al., 2005). Furthermore, this investigation found evidence of a dose-response relationship between social fragmentation and first-ever admission rates for psychosis (Allardyce et al., 2005). Another investigation found that independently of individual characteristics, higher levels of neighborhood social fragmentation (indexed by proportion of single persons and divorced persons) predicted increased schizophrenia incidence, which was attributed to increased experiences of social isolation (Van Os, Driessen, Gunther, & Delespaul, 2000). Other studies operationalized social fragmentation in terms of population turnover, finding increased incidence of schizophrenia among areas with low social cohesion (Silver, Mulvey, & Swanson, 2002). In contrast, high social cohesion is a candidate protective factor against psychosis risk. For example, higher levels of neighborhood social cohesion were found to be protective against childhood psychotic symptoms in victimized children (Crush et al., 2017).

4.2 Discrepancy intermediary mechanisms

Income inequality, ethnic density, and social fragmentation share facets through which prolonged exposure could have a damaging impact. A sizeable portion of these shared facets can be conceptualized in terms of degrees of social capital. Social capital reflects the value of social networks to individuals and society (Bourdieu, 1986). Social capital can be defined as the extent and quality of an individual’s social networks, mutual trust, and enacted social norms of reciprocity and support (Coleman, 1988). A key facet of social capital constitutes a sense of belonging to a certain group, or network of individuals (Butler & Muir, 2017; Nawyn, Gjokaj, Agbényiga, & Grace, 2012; Oliver & Cheff, 2014; Schellenberg, Lu, Schimmele, & Hou, 2018). Social capital has been intricately linked to health and life satisfaction (Elgar et al., 2011).

A wide body of epidemiological literature has shown that income inequality, which affects social capital, is similarly associated with poor mental and physical health and well-being (Elgar, Gariépy, Torsheim, & Currie, 2017; Karlsdotter, Martín, & del Amo González, 2012; Pickett & Wilkinson, 2015; Vilhjalmsdottir, Gardarsdottir, Bernburg, & Sigfusdottir, 2016). Income inequality at the neighborhood, state and country level, for one, has also been shown to elicit chronic feelings of distrust and lack of social cohesion, which are then associated with negative health outcomes (Bjornstrom, 2011; Fairbrother & Martin, 2013; Rözer & Volker, 2016). Further, emerging investigations have observed that early chronic exposure may be particularly impactful with regards to health and life satisfaction (Elgar et al., 2017). Thus, income inequality may impact feelings of trust, belonging, and social cohesion on a pervasive level.

There is evidence that ethnic density could impact mental health outcomes through a similar mechanism. Much like income inequality, low ethnic density creates a feeling of *discrepancy*, imposing roadblocks toward building social capital. Indeed, low ethnic density has been long proposed as a harmful influence for building social capital, which has in turn been linked to adverse physical and mental health outcomes (Eliacin, 2013; Yang, Lei, & Kurtulus, 2018). Low ethnic density has also been shown to deeply impact sense of belonging and community, which was related to psychiatric disorder incidence (Emerson, Minh, & Guhn, 2018; Finney & Jivraj, 2013; Pan & Carpiano, 2013).

Social fragmentation, like the previously discussed factors, is an additional key factor for impeding building of social capital. Social fragmentation could lead to experiences of social isolation, resulting in feelings of lack of trust and belonging, along with reduced social support (Eliacin, 2013; Van Os et al., 2000). Conversely, increases in the counter to social fragmentation, social cohesion, are associated with decreased psychological distress even after controlling for factors such as neighborhood socioeconomic status (Erdem, Prins, Voorham, Van Lenthe, & Burdorf, 2015). Thus, structural exposures in the *discrepancy* domain, putatively impeding the building of social capital could particularly impact the marked social deficits facet of psychotic disorders (Addington, McCleary, & Munroe-Blum, 1998).

4.3 Discrepancy neural mechanisms

Structural exposures in the “*discrepancy*” domain thus share overlapping components of impacted social capital, including lack of social cohesion, an impacted sense of trust and belonging, as well as less robust social networks and sense of support. There are several solid candidates as to biological systems that could be impacted by the above-mentioned exposures. One of these is the oxytocinergic system. The oxytocinergic system relates to social processes such as social attachment, empathy, and social threat (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Norman, Hawkley, Cole, Berntson, & Cacioppo, 2012). There is evidence of intranasal oxytocin attenuating amygdala-brainstem coupling in the face of threatening social stimuli (Kirsch et al., 2005). Studies have also found intranasal delivery of oxytocin to modulate evaluation of socially relevant faces through the amygdala (Gamer, Zurowski, & Büchel, 2010) and fusiform gyrus (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Petrovic, Kalisch, Singer, & Dolan, 2008). Oxytocin has been linked to

increased in-group trust (De Dreu et al., 2010; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005) as well as to elevated processing of positive social information (Di Simplicio, Massey-Chase, Cowen, & Harmer, 2009; Guastella, Mitchell, & Mathews, 2008). There is further evidence in the animal literature of increased oxytocin blunting social vigilance behavior, suggesting increased manifestations of trusting behavior (Ebitz, Watson, & Platt, 2013). Notably, there is evidence for a degree of specificity with regards to oxytocin modulating affective social processes. For example, while oxytocin has been found to decrease emotional arousal to threatening human stimuli, this was not the case for threatening animal stimuli, or for general positive/negative valence stimuli (Norman et al., 2011).

Speaking beyond oxytocin, neuroendocrine and autonomic nervous system alterations are other mechanisms through which lack of trust, belonging, and social capital could modulate adverse mental health outcomes (Norman et al., 2012). Neural regions involved in processing of social threat, rejection, and lack of belonging include the amygdala, orbitofrontal cortex, and ACC (Adolphs, 2009; Eisenberger, Lieberman, & Williams, 2003). These regions project to brainstem nuclei which regulate parasympathetic and sympathetic outflow (Critchley, 2005). Autonomic nervous system engagement can change based on high-level processing from these regions that also regulate processing of social threat, rejection, and lack of belonging. Given the responsivity of the autonomic nervous system to these socio-psychological contexts, chronic signaling from implicated regions could confer alterations in these circuits over time (Berntson, Cacioppo, Quigley, & Fabro, 1994). This notion is supported by investigations on individuals experiencing chronic loneliness, which exhibit alterations in autonomic reactivity across various contexts, leading to poorer physical and mental health outcomes over time (Cacioppo et al., 2002; Hawkley, Masi, Berry, & Cacioppo, 2006).

Studies have theorized social disconnection (both the perception/possibility of social disconnection and the experience of social disconnection/exclusion) to be processed by neural systems responsible for responding to harm and impending danger. This hypothesized “neural alarm system” includes the amygdala, as well as the dorsal ACC, anterior insula and periaqueductal gray (PAG), which are responsible for pain-related processing (Eisenberger & Cole, 2012). Chronic activation in these regions can trigger endocrine and autonomic responses that can negatively impact health over time. Conversely, vmPFC and posterior cingulate cortex (PCC) are involved in processing safety detection and fear, and increased activity in these regions may inhibit sympathetic and promote parasympathetic responses, which is protective for physical and mental health (Eisenberger & Cole, 2012). Dysregulation in these regions due to chronic stress exposure thus could possibly compromise these protective processes. Taken together, social neuroscience literature allows us to gain a fuller understanding of mechanisms through which the structural exposures in the “*discrepancy*” domain (income inequality, ethnic density, social fragmentation) could impact neurological systems over time. Nonetheless, future studies will be crucial in marrying the literature exploring psychosis incidence rates in light of these exposures, with the non-clinical literature exploring neural correlates of possible intermediary causal mechanisms (such as reduced social cohesion, sense of belonging, trust, and reduced social capital).

5. Deprivation structural exposure

5.1 Deprivation definition and relations to psychotic disorder risk

The “*deprivation*” dimension is characterized by environmental and neighborhood conditions with a lack of appropriate resources with regards to factors such as employment, income, education, health, living conditions, and barriers to housing and services. While exposure to these environments has been associated with a host of negative health outcomes, there is evidence that living in a high *deprivation* environment can confer increased risk for developing a psychotic disorder specifically (Bhavsar et al., 2014; Bhavsar, Fusar-Poli, & McGuire, 2018; Kirkbride et al., 2012; Lasalvia et al., 2014; O’Donoghue et al., 2015; Omer et al., 2014). Two studies used an overall *deprivation* index including employment, income, education, health, *deprivation* in living conditions, as well as barriers to housing and services (Bhavsar et al., 2018; Kirkbride et al., 2012). These studies found consistent results, with the most deprived neighborhoods having a significant increase in incidence rate of psychosis risk status (Bhavsar et al., 2018; Kirkbride et al., 2012). Another investigation incorporated area income and employment *deprivation*, health *deprivation* and disability, education, skills and training *deprivation*, barriers to housing and services, and living environment *deprivation* (Bhavsar et al., 2014), finding a similar pattern of increased schizophrenia incidence among those living in high *deprivation* areas. Yet another study focused on material *deprivation*, finding greater rates of psychotic disorders in those exposed to material *deprivation* (Omer et al., 2014). It is key to note that though factors such as population density could relate to overall *deprivation* in certain regions, there is research suggesting that the association between high *deprivation* and schizophrenia incidence holds even after controlling for these factors (Bhavsar et al., 2014).

5.2 Deprivation intermediary mechanisms

While there are different types of *deprivation*, all share the aspect of a need or resource that is not being provided, possibly affecting adaptive neurodevelopment and ongoing neural function in an individual. That is, there is a lack of species- and age-typical complexity in environmental stimuli (McLaughlin, Sheridan, & Lambert, 2014). Thus, *deprivation* can be conceptualized as chronic exposure to environments that lack adequate stimulation for an individual. Chronic lack of needed educational, cognitive, economic, or health resources can lead to neural under-stimulation in certain key functions, which in turn could negatively impact neurodevelopment. This is especially the case during childhood, adolescence and early adulthood, which are marked by critical periods of neurodevelopment (Pechtel & Pizzagalli, 2011; Shaw et al., 2008). The literature has long observed an association between exposure to *deprivation* and health outcomes (Bak, Andersen, & Dokkedal, 2015). Prolonged exposure to *deprivation* has been associated with adverse mental health outcomes, including increased psychotic symptoms such as paranoia, as well as depressed symptoms (Wickham, Taylor, Shevlin, & Bentall, 2014). *Deprivation* exposure has also been associated with increased risk of hypertension, among other physical health outcomes (Matheson, Moineddin, & Glazier, 2008).

On the other hand, animal studies have shown that continued exposure to enriched, complex environments (the counter to environments high in *deprivation*) yields greater

neurobiological resilience (Bardi et al., 2016; Lambert, Nelson, Jovanovic, & Cerdá, 2015). Neurobiological resilience was evidenced, for instance, through less observed anxiety in response to exposure to novel objects, less anxiety-typical behavior in response to a predator odor, as well as decreased amygdala activation following a water escape task designed to induce high stress levels. Lastly and importantly, exposure to *deprivation* (in the form of low socioeconomic status) has marked effects on cognitive performance for complex tasks, including language (Fernald, Marchman, & Weisleder, 2013; Weisleder & Fernald, 2013) executive function and memory (Evans & Schamberg, 2009; Farah et al., 2006; Hackman, Farah, & Meaney, 2010; Hackman, Gallop, Evans, & Farah, 2015; Kishiyama, Boyce, Jimenez, Perry, & Knight, 2009; Noble, McCandliss, & Farah, 2007). Markedly, these differences have been found to be mediated by a lack of exposure to enriching and complex activities in childhood (Bradley, Corwyn, McAdoo, & García Coll, 2001; Linver, Brooks-Gunn, & Kohen, 2002; Yeung, Linver, & Brooks-Gunn, 2002).

5.3 Deprivation neural mechanisms

Exposure to *deprivation* is likely to impact neural development through several key mechanisms. There is strong evidence of an impact of low environmental complexity on cortical development; an effect which has been observed in both the animal and human literature (Diamond, Rosenzweig, Bennett, Lindner, & Lyon, 1972; Leporé et al., 2010). Early and chronic exposure to low complexity environments may yield neural systems selectively designed to best process low complexity environments (McLaughlin, Sheridan, & Lambert, 2014). This, in turn, could yield long-term adverse mental and physical health outcomes when the individual inevitably has to adapt to a high-complexity environment and demands. The process through which environmental stimuli impacts neurodevelopment likely stems from central nervous system pruning of synaptic connections, deemed the “selective elimination” hypothesis (Changeux & Danchin, 1976; Huttenlocher, de Courten, Garey, & Van der Loos, 1982; Petanjek et al., 2011). There is an overabundance of synaptic connections that are initially created (i.e., synaptic proliferation), and these are pruned across development to accommodate and adapt to the being’s needs. Pruning following synaptic proliferation ensues throughout childhood and adolescence (Huttenlocher, 1979; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986). Theoretically, this leads to an adaptive system whereby only the most environmentally helpful and efficient synaptic pathways remain. However, if the environment lacks adequate enrichment, chronic and early exposure to low complexity environments could foster excessive pruning, resulting in a lower number of synaptic connections, along with lower dendritic branching. Brain regions with protracted developmental trajectories, making them more sensitive to environmental influence, would be particularly likely to be impacted by exposure to *deprivation*. This includes the association cortex (Gogtay et al., 2004) and PFC (Pechtel & Pizzagalli, 2011). The association cortex refers to lateral and medial prefrontal, parietal, and temporal areas of the cortex involved in cognitive processing (Dumontheil, Thompson, & Duncan, 2011; Mountcastle, Lynch, Georgopoulos, Sakata, & Acuna, 1975; Pulvermüller & Garagnani, 2014).

Though the association cortex engages in stimuli processing across multiple sensory modalities, it is also necessary for higher-level cognitive functions including language,

executive function, and social cognition (Badre & D'Esposito, 2009; Culham & Kanwisher, 2001). Likewise, the PFC is chiefly involved in executive and affective regulatory functions (Pechtel & Pizzagalli, 2011). As alluded to earlier, the animal literature yields strong support for this interpretation. For example, global *deprivation* in rodents has been documented to result in decreases in dendritic arborization and spines throughout the cortex, as well as decreases in total brain volume (Bennett, Diamond, Krech, & Rosenzweig, 1964; Diamond et al., 1966; Globus, Rosenzweig, Bennett, & Diamond, 1973). These changes become more widespread and persistent the longer the exposure to the *deprivation* environment.

The human literature, though needing further studies in order to increase specificity of affected regions and degree of stability of the effect, paints a similar picture. Much of this literature has emphasized socioeconomic status. Though investigations of neighborhood socioeconomic status have been more scarce, low parental socioeconomic status has been associated to lower exposure to enriching cognitive experiences in the school and home environment (Bradley et al., 2001; Sirin, 2005). Conversely, cortical gray matter volume as well as cortical thickness has been found to be greater in students from higher-income backgrounds, with certain regions of the association cortex relating to greater academic performance (Mackey et al., 2015). Low socioeconomic status has been associated with decreased volume in the association cortex, particularly in PFC (Noble, Houston, Kan, & Sowell, 2012; Noble et al., 2007). Low socioeconomic status has also been associated with more diffuse patterns of activation in the association cortex while supporting performance on executive function and language tasks in children (Raizada & Kishiyama, 2010) and adults (Gianaros et al., 2008; Gianaros & Manuck, 2010). A perhaps more extreme *deprivation* exposure that has been covered in the literature is that of institutionalization, which often constitutes a clear scarcity of social and cognitive inputs, ranging from maternal care *deprivation*, lack of variation in daily routines and experiences, enriching cognitive stimuli (such as books or toys) to peer interaction opportunities (Gee et al., 2013; Nelson, Furtado, Fox, & Zeanah, 2009; Smyke et al., 2007; Tottenham, 2012; Tottenham et al., 2010). Here, too, findings have been consistent, whereby institutionalization has been associated with decreases in gray matter thickness and volume, along with cognitive dysfunction (McLaughlin et al., 2014; Mehta et al., 2009; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012). While further synthesis of the research is needed in order to solidify the theorized association between increased psychosis incidence and structural exposures related to *deprivation*, the literature in animal and non-clinical human populations offers us a theoretical framework of possible affected neural mechanisms.

6. Stimulation discrepancy deprivation model of psychosis summary

Partially inspired by diathesis-stress conceptualizations of psychosis, the SDD model distinguishes itself in highlighting the critical importance of systems-level considerations for assessing both pre-existing biological underlying vulnerabilities, and exposure to chronic stressors going into adolescence and young adulthood (Fig. 2). The SDD model is also novel in proposing three distinct types of structural exposures, along with neural underpinnings and intermediary mechanisms. We pose that exposure to structural stressors can bring about pre-existing neurobiological vulnerability through prolonged exposure during the pre-natal, early post-natal, and childhood periods. Structural stressors can then additionally contribute

to increasing vulnerability throughout adolescence and young adulthood. Chronic exposure to structural stressors throughout adolescence and young adulthood can drive a cascade of HPA dysregulation, aberrant dopamine and glutamate neural transmission, as well as altered brain function and development, ultimately driving increased inflammation, cognitive and social dysfunction, altered glucocorticoid receptor function, among other factors specific to the three structural exposure types, eventually leading to onset of psychotic symptoms (Fig. 2). Structural stressors thus are key to consider in chronic stress models of psychosis, as they are liable to be critically relevant throughout the lifetime with regards to providing detrimental or protective influences on the individual.

7. Future directions

The present review drew on empirical evidence from the neuroscience literature, as well as from epidemiological evidence of structural exposures in order to propose intermediary mechanisms as well as neural underpinnings through which structural stressors could impact risk for developing a psychotic disorder. It will be necessary to directly test these theories in populations across the psychosis spectrum. Further, specifying sensitive and critical developmental periods during which these exposures could be particularly impactful is a critical future direction. Models testing both cumulative and distinct effects of these exposures would also be beneficial. Examining the interplay between individual and structural level stressors is also important in order to compare degrees of impact and decrease noise due to individual differences. Finally, further identifying and increasing understanding of buffering or protective environmental factors will aid in conceptualizing psychosis risk profiles. In conclusion, in the present review, we pose that system, or structural level factors deserve more attention within psychological research. It is crucial to enhance our understanding of manners in which structural factors may exert influence on their own, and through facilitating the expression and exacerbation of individual vulnerability (biological factors, genetic predispositions, individual behaviors, cognition and personality) (Glass & McAtee, 2006; Rose, 2001). Given their standalone influence and key role in facilitating expression of individual pre-existing vulnerability, targeting these system level conditions through epidemiological, public health approaches may ultimately exert a greater impact on an aggregate, societal level.

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Fig. 1.
The stimulation, discrepancy, and deprivation model: structural exposures, intermediary mechanisms, and biological mechanisms.

Fig. 2.

The stimulation, discrepancy, and deprivation model as it relates to psychotic disorder onset.