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Editorial

Childhood trauma and psychosis: Moving the field forward

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There is now overwhelming evidence that early adversity increases the risk of later psychopathology. In fact, the risk of depression, anxiety and psychotic disorders is increased in individuals exposed to a range of early adverse experiences (physical and sexual abuse, psychological neglect, early separation from parents, bullying) and adverse social contexts (social fragmentation, high population density). While these events have been recognised as important risk factors for depression for decades, their role as risk factors for psychosis has recently gained considerably more attention.

Over the last few years, however, evidence has accumulated to indicate that early adverse experiences play a significant role not only in increasing the risk of developing psychosis, but also in its course and outcome (Trotta et al., 2015). Furthermore, data also suggest that there may be a dose-response relationship between number and severity of adverse events and risk, severity, and chronicity of psychotic disorders (Li et al., 2016; Morgan and Gayer Anderson, 2016).

Although this body of literature has focused on early adversity as a factor to study, there is, as highlighted in a recent Nature review, "a pressing need to understand how maltreatment increases the risk of psychiatric disorders" (Teicher et al., 2016). Furthermore, a better understanding of the biological mechanisms through which early trauma contributes to the development of psychiatric disorders will be fundamental to identifying possible targets for intervention and prevention strategies.

This need prompted our interest in putting together this special issue, with articles that explore the specific role that childhood trauma and adversity play in psychosis presentation and subsequent course, with a specific interest in the role of timing and severity, and beyond this, on the possible mediators and mechanisms that underlie its role.

In the first article of the issue, Schalinski et al. (in this issue) examine the role of both severity and timing of various types of adversity, experienced both in childhood and in adulthood, on the exacerbation of positive and negative symptoms in 180 patients with psychotic disorders, 75% of whom had a diagnosis of schizophrenia. Interestingly, they also evaluated the role of dissociative symptoms as a possible mediator of this relationship. This study, which rated the age at which each adverse event occurred, shows that there is not only a dose-response relationship between adversity and positive symptoms, but that timing of occurrence is crucial, with severity of neglect at age 10 being specifically associated with more severe positive psychotic symptoms. These authors also show that the presence of dissociative symptoms mediates the relation between trauma load in childhood and positive symptoms in adulthood. It is interesting that there is no relationship between trauma and negative symptoms in this study, suggesting that the impact of early adversity may be specific to the pathophysiology that underlies the production of positive symptoms, perhaps pointing to the different neurobiological basis that may underlie these groups of symptoms.

In the second article of the issue, by Loewy et al. (in this issue), we can understand more about the issue of timing of exposure and relationship with symptoms. This article focuses on a population at the lower end of severity, of young individuals at increased risk of psychosis but not yet ill. In this group, aged 12 to 30 years, the authors find that 61% of participants reported exposure to traumatic events, and that in almost all cases this preceded the onset of the clinical high risk syndrome and occurred before the age of 12. Similarly to what previously reported in patients with the established illness, these authors find that the history of trauma is associated with significantly more severe perceptual disturbances and general and affective symptoms, as well as with lower levels of functioning. Consistently with literature on frank psychotic symptoms, there seems to be a cumulative effect of trauma on psychopathology in this sample, with the higher number of interpersonal traumatic events being significantly correlated with more severe suspiciousness, perceptual abnormalities, general and affective symptoms, and again lower level of functioning.

Together, these two first articles stimulate the discussion on what could be the possible mechanisms that underlie the relationship between early trauma and adversity, and specific symptoms, especially in the positive group. Several hypotheses have been put forward, including those relating to cognitive style and appraisal, and these are some of the potential mechanisms examined by the next articles.

Gibson et al. (in this issue) simultaneously test several cognitive mechanisms as potentially relevant to the relationship between exposure to traumatic life events and psychotic-like experiences. They particularly focus on perceived stress, dissociation, negative self-schemas, negative other-schemas, and/or external locus of control as mediators of this association, and provide strong justification for selecting these specific mechanisms. As in the previous article, this study also reports from non-ill individuals, in this case a large sample of 945 students aged 18 to 34. In this student population, 33% of individuals were positive for a childhood adverse experience. The authors find that greater perceived stress, dissociation, external locus of control, and negative self- and other schemas all had significant indirect effects on the relationship between trauma exposure and more psychotic-like experiences, both independently and in a multiple mediator model. It is interesting that in a second set of analyses, they found that only dissociation remained as a significant mediator when comorbid psychological

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symptoms were taken into account in the analysis. This finding is particularly interesting when considering that the first article in this issue also found, in a clinical population, dissociative symptoms as mediators of the relationship between trauma and symptoms severity. These findings make a strong case for the need to target dissociative tendencies in the aftermath of trauma exposure, as well as other trauma-related cognitions (stress sensitivity, maladaptive schemas, externalizing attributional styles), as a way to help reducing the risk for psychopathology, possibly beyond psychosis.

Pan et al. (in this issue) tested the role of a different set of factors, specifically positive social and personality characteristics ('positive attributes'), as mediators of the relationship between childhood trauma and emergence of psychotic experiences. They present longitudinal data from a very large cohort of 2511 Brazilian community adolescents (and their parents), first evaluated at age 12 and reassessed after 3 years. In this study, childhood trauma was evaluated according to both the child self-report, and the parent report. These authors find that these positive attributes mediates the association between childhood trauma and adolescent psychotic experiences, and were negatively associated with the emergence of such experiences. This points to the fact that there are positive social and behavioral traits already evident in childhood that may reduce the likelihood of later psychopathology, and that could also be the target for psychological and psychosocial preventive interventions in children at risk.

In the final article of this first part, Pruessner et al. (in this issue) investigate the role of another important factor, sex, in the relationship between early adversity and symptomatic and functional outcome. They present a longitudinal study of 210 patients with first episode psychosis, where psychotic symptoms and general functioning were evaluated at baseline and again after 12 and 24 months. The role of different types of abuse was examined separately, revealing that emotional abuse had the strongest predictive value for depressive and positive symptoms, and for global functioning. In contrast, emotional neglect best predicted negative symptoms in male patients at the two-year follow-up. Preliminary findings from this study also suggest that male patients who experienced trauma show no improvement in levels of functioning over time. These results would suggest the presence of a different sex-related vulnerability to the stress induced by the experience of early adversity, pointing to the importance of evaluating the stress response also in a neurobiological framework.

This topic allows us to transition smoothly to the second part of this special issue, which includes articles focused on the possible biological mechanisms and pathways affected by childhood trauma in patients with psychosis.

The article from our group, by Ciufolini et al. (in this issue) investigates the effects of childhood abuse on the activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis, one of the main biological systems involved in the response to stress, in patients with first episode psychosis. The study evaluates a sample of 169 first episode psychosis patients and 133 controls and finds a divergent effect of severe childhood abuse on HPA axis activity in patients and in controls. More specifically, patients with severe childhood abuse show a lower cortisol awakening response while controls with severe childhood abuse present higher cortisol awakening response. The diverging effect between patients and controls is particularly interesting as it suggests that a less reactive HPA axis following the exposure to severe childhood abuse may predispose to the development of psychosis, while a more reactive HPA axis may be protective in this context.

Aas et al. (in this issue) explored another possible biological mechanism that may mediate the link between childhood trauma and psychosis. In particular, their study examined levels of BDNF, a neurotrophic factor that plays a major role in neurogenesis and neuroplasticity, in a large sample of patients with schizophrenia and healthy controls. The authors confirm the overall reduced plasma levels of BDNF in patients when compared with controls, but more importantly they report a stronger reduction in levels of BDNF in patients with experience of childhood sexual abuse. Furthermore, they identify an association between reduced levels of BDNF and increased number of depressive episodes, suggesting a possible role of lower levels of BDNF in the development of depressive symptoms in patients with schizophrenia.

The following two articles by Trotta et al. (in this issue) and Lecei et al. (in this issue) explore the role of the interaction between genetic predisposition and exposure to childhood adversities in determining psychosis. Indeed, a biological (genetic) pre-existing vulnerability has often been hypothesized to try and understand why some people but not others exposed to childhood adversities develop psychotic disorders. The two articles approach this issue with different methodologies. First, Trotta et al. focus on specific genetic polymorphisms known to affect dopamine levels (COMT Val^{158} Met, AKT1 rs 2494732, and DRD2 rs1076560) and on their interaction with childhood adversities to explain onset of psychosis. The findings from this study do not provide evidence for a role of these candidate genes in modifying the association between childhood trauma and development of psychosis. In the second article, Lecei et al. (in this issue) use a monozygotic twin differences approach to test whether differences in exposure to childhood trauma among twins are associated with differences in symptoms. The authors find that larger differences in childhood trauma exposure among monozygotic twins are associated with greater differences in the expression of psychiatric symptoms, suggesting that the association between childhood trauma and psychiatric symptoms is a genuine one and is not uniquely related to gene-environment correlations.

In the final article of this special issue, Cattane et al. (in this issue) use an hypothesis-free and cross-tissue, cross-species approach to identify specific microRNA (miRNA) signatures associated with early adversities, which could explain the vulnerability to develop schizophrenia following childhood trauma. The authors initially identify specific miRNA which are down-regulated both in blood samples of human subjects exposed to childhood trauma, in the brain of rats exposed to prenatal stress, and in human hippocampal progenitor cells treated with cortisol. Interestingly, the authors find down regulation of specific miRNA (miR-125b-1-3-p) detected from the previous experiments also in patients with schizophrenia exposed to childhood trauma, suggesting this specific miRNA may represent a key marker associated with increased risk of schizophrenia following exposure to childhood trauma.

In conclusion, we believe the studies included in this Special Issue investigate some of the key questions related to the link between childhood trauma and psychosis, ranging from the identification of relevant time windows for this association, to the biological mechanisms involved in this link, and ultimately moving the field forward with the identification of biological and psychological targets for future effective preventative and treatment strategies. With this Special Issue, we aimed to take one step forward in highlighting the importance of this area of research, and we hope that the psychiatric research community will continue to generate more data to bolster our understanding of the complex association between childhood trauma and psychosis, and ultimately contribute to preventing severe psychiatric illness and to achieving a better mental health for children exposed to various traumatic events.

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