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Not just risk: there is also resilience and we should understand its neurobiological basis

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In this Issue of Schizophrenia Research, the paper "Risk and resilience brain networks in treatment-resistant schizophrenia" by Ganella et al. (2017) has refreshingly focused not only on investigating which brain networks may confer risk to schizophrenia, but also which ones may confer resilience to the illness in individuals who have a genetic vulnerability but remain well.

The paper presents data from a cross-sectional neuroimaging study conducted on individuals with treatment resistant schizophrenia, unaffected first-degree family relatives of patients with this diagnosis, and healthy controls. In this sample, the authors used functional Magnetic Resonance Imaging (fMRI) to evaluate whether resting-state functional brain connectivity (rs-FC) could represent a risk or resilience endophenotype for schizophrenia. Indeed, resting state is an approach that can be useful to evaluate the brains functional organization and its alterations across diseases. The Authors' choice was dictated by accumulating evidence that in individuals with schizophrenia there is often a decrease in resting state signal or functional connectivity, particularly in medial, dorsolateral and ventrolateral prefrontal cortex, and temporal lobe, as highlighted in a recent review published in this journal (Mwansisya et al., 2017). However, in individuals at illness onset and in those "at risk" of the disease, for example because of a genetic vulnerability conferred by having an affected first degree relative, the evidence from resting state studies has been less consistent, with some studies reporting decreased, and others increased, connectivity of the same brain areas often reported as decreased in individuals with established schizophrenia.

Elegantly, this paper sought to identify not only brain networks indicative of risk for schizophrenia, but also any unique brain network indicative of resilience in the unaffected relatives of patients with a particularly severe form of the disease, treatment resistant schizophrenia. They additionally evaluated the efficiency of such networks, with measures that quantify the network ability to exchange information, either at neighbour or whole network level.

The findings of the paper are interesting in that both patients and unaffected relatives were found to share several reductions in resting state connectivity, particularly in temporal and occipital lobes, which were operationalised as schizophrenia risk markers. In contrast, alterations unique to the unaffected relatives were much rarer. These were mostly circumscribed to temporal and subcortical areas, particularly middle temporal pole and posterior cingulum. The authors also found that in both patients and unaffected relatives, compared to controls global efficiency of the network was reduced. Interestingly, this is a finding that is consistent with our recent structural imaging reports of reduced structural global efficiency and less integrated networks in patients with a first episode of schizophrenia and other psychoses who do not respond to treatment in the first 12 weeks after illness onset (Crossley et al., 2017; Palaniyappan et al., 2016).

The Authors attempt to evaluate networks that may underlie resilience is particularly valuable, as it tries to fill a critical gap in the literature. We have seen, over and over again, that risk for schizophrenia is associated with almost every risk factor associated with psychiatric diseases. We have seen these varying from genetic vulnerability, to childhood trauma and life events, to obstetric complications, immunological activation, social deprivation, urbanicity, illicit substances and so on. For example, we have recently shown that early and life trauma, and immune activation are associated with psychosis, and furthermore, that immune activation and an altered biological response to stress particularly characterise those individuals who do not respond to treatment (Mondelli et al., 2011; Mondelli et al., 2015). We have however been unable to establish, or even to start establishing, why so many individuals exposed to these risk factors do not develop the disorder. While measures of increased risk, like odds ratios and relative risk, may be informative, they tell us very little as to what protects exposed individuals from becoming unwell.

In mental health, resilience is a term often used in the context of the long- and short-term consequences of severe adversity and extreme trauma. Still, while we have excellent operational definitions and measures of adversity, we lack a common and reliable definition of resilience. When thinking of resilience in the context of neurobiological

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systems, the definition provided by Ann Masten, internationally known for her work on competence, risk and resilience, and child development seems most appropriate. She refers to resilience as "the capacity of a dynamic system to adapt successfully to disturbances that threaten the viability, the function, or the development of that system" (Masten, 2014). In this framework, the neurobiological basis of resilience could represent the crucial system linking vulnerability and experience on one side, and the emergence of the illness and its adverse outcomes on the other side. Interestingly, 75% of cases of adult mental illnesses, such as schizophrenia, depression and bipolar disorder, emerge before the age of 18 years, with 50% evident before age 15 (Kim-Cohen et al., 2003). This points to late childhood and adolescence as times when risk and resilience factors may impact most on brain developmental trajectories, to eventually give rise to mental disorders. Studying brain maturation, with a longitudinal approach, could truly advance our understanding of how a dynamic and evolving system like the brain may be shaped differently to give origin, or offer resilience, to the onset of mental health problems. In this sense, resilience could be considered as a process, resulting from the engagement of the individual with its environment (Southwick et al., 2014). In this framework, the presence of a genetic vulnerability and a history of early adversity could push neurobiological systems -including the brain- to develop differently than in those individuals with the same vulnerability, but with the buffer effect of growing up in a warm and safe environment.

Studies like the one published in this issue of the journal can move us closer to understanding the mechanisms of resilience. Still, to better understand what protects vulnerable individuals from developing the disorder, or to recover from it, we need to establish how experience, environment, and biological systems interact at ages that are crucial for neurodevelopment. These times represent pluripotent risk phases, when a number of subsequent psychopathological outcomes are possible. Investigating the brain determinants of poor and good mental health in these periods could help identify the specific trajectories that confer risk and require interventions (psychological or pharmacological), and distinguish them from those that safeguard against adverse mental health outcomes.

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Conflict of interest

I have no conflict of interest to declare.

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