Gene–Environment Correlation for Schizophrenia and Major Depression

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Both genetic and environmental risk factors are involved in the aetiology of schizophrenia (SCZ) and major depressive disorder (MDD). Importantly, environmental and genetic risk factors are often related as evidenced in gene–environment correlation (rGE), which describes the observation that genetic and environmental factors are associated with each other.

Keywords: environment ; schizophrenia ; major depressive disorder ; genetics ; gene–environment correlation

1. Introduction

A complex interplay between genes and the environment has been well established in the aetiology of psychopathologies [1][2]. One form of this intricate interplay is referred to as gene–environment correlation (rGE), which is traditionally understood to get stronger over time as individuals more actively select their own environments based on their genetic propensities [3][4].

The prevalence of SCZ and MDD with 1% and 16–20%, respectively, is well established in adults [5][6][7]; however, we know only little about these two psychopathologies, particularly SCZ, in children. This is primarily due to an age of onset in late adolescence or early adulthood for both disorders [8][9], thus making early diagnosis difficult. The limited number of epidemiological studies estimate a prevalence of childhood-onset SCZ between 1 in 30,000 to 1 in 40,000 children [10][11]. However, the prevalence of MDD in childhood and adolescence is slightly higher, ranging from 0.87% to 1.43% in pre-school children [12] to an overall prevalence of 0.4–2.8% in children and 0.4–8.3% in adolescents [13][14].

2. Genetic Influences

Both SCZ and MDD have substantial heritability estimates in adults with twin and family studies approximating ~80% [2][15] and ~38% [16][17] for SCZ and MDD, respectively. Whilst few studies have assessed the heritability of SCZ in children, Rutter et al. (2006) [18] suggest that the heritability of MDD is at a low level in children and increases to moderate levels in adolescents and then stays relatively stable until adulthood.

Further, the genetic architecture of both psychopathologies is highly polygenic, consisting of thousands of single nucleotide polymorphisms (SNPs) [19]. Although the effects of each single SNP are very small, these can be combined into Polygenic Risk Scores (PRS) consisting of the weighted sum of the risk-associated alleles to estimate the genetic propensities to these psychopathologies for each individual [20][21].

3. Environmental Influences

PRS-based methods are a useful tool to investigate gene–environment interplay given that SCZ and MDD are not just influenced by genetic but also by environmental risk factors, which themselves have been found to be heritable [2][19][22][23]. These environments can range from a short gestational period [24][25] and low parental educational attainment [26][27][28] in childhood, all the way to unemployment [22][29], low socio-economic status (SES) [30][31] and death of a spouse [32] in adulthood. However, environmental exposures are often influenced by individual behaviors, these behaviors will in turn often change as individuals transition from one developmental period to another. For instance, differences in temperament in early childhood lead to considerably bigger differences in antisocial behavior in adolescences [33]. Moreover, socio-cultural influences, such as changes in smoking behavior due to tobacco availability, further contribute to potentially differential exposures to environmental risks over time [34]. Nevertheless, studies need to focus not just on understanding the impact of the timing but also the effect of continuous adverse environmental exposures on the liability to psychopathology [35].

4. Psychopathology across Development

Early environmental exposures or events, including adversity and stress, can have lasting effects on our biology depending on the timing of these events during critical developmental windows [23][36]. Whilst the importance of a life-course perspective in psychiatric outcomes is generally well understood, investigating psychopathological outcome over time requires not just longitudinal data but also large samples [37]. Additionally, the divide between child and adult behavioral research and associated clinical services has often been a barrier to adopting a developmentally-focused approach [37]. Bearing in mind that half of all mental health lifetime cases occur by the age of 14 and 75% by 24 years, with late onset mental health outcomes often being a co-morbidity [38], this raises the question, not just what the environmental targets for treatments or preventions are, but also if these targets change as individuals transition from childhood to adulthood. This is further complicated by the heterogenous symptomology for some psychiatric disorders, such as for SCZ and MDD, during different developmental stages [8][9][18]. For instance, SCZ phenotypes range from autistic symptoms and cognitive disabilities in childhood [39][40] to anxiety in adolescents [41], whilst MDD often manifests itself as irritable mood, lack of weight gain and anhedonia in children [42], to subthreshold depressive symptoms in pre-adolescents [43].

5. rGE across Development

From a perspective of rGE, genetic risk variants can influence the *exposure* to environmental factors through either *passive* rGE, when parents pass their genes to their offspring whilst also shaping their environment; *active* rGE, whereby a genetically influenced behavior predicts the probability of exposure to an environmental factor; or *evocative* rGE when a genetic predisposition modulates an individual's behavior which then evokes a response from others [4]. It has further been suggested that there is a developmental shift from passive rGE to evocative and active rGE occurring between infancy and adolescence as children start to more actively shape their environments [3], with active rGE being more prevalent later in life compared to evocative [44]. For instance, a recent study investigated the correlations of several socio-environmental factors, including urbanization, and the PRS for SCZ and MDD (amongst others) in 2232 British twins who were born between 1994–1995 and followed up until age 18 in the Environmental Risk Longitudinal Twin Study [45]. There was some evidence to suggest that rGE increases across childhood, whereby associations between the PRS for SCZ and urbanicity and between the PRS for MDD and deprivation increased over time as the children got older [45].

A longitudinal analysis of PRS in three British community cohort studies showed that rGE for SCZ and MDD remained largely stable in childhood and did not change considerably, except for one marker of low SES for SCZ. Moreover, the strength of rGEs in adulthood only changed for one indicator of urbanization for SCZ and two markers of low SES for MDD. Moreover, by investigating rGE changes between childhood and adulthood in NCDS, the genetic liability to SCZ and MDD on SES increased across the life course for both psychopathologies, as well as decreasing for rented accommodation for MDD. However, effect sizes for all significant findings were small and therefore the findings must be interpreted with caution. rGE changes over time are likely disorder specific.

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