Assessing the impact of environmental factors on the adolescent brain: the importance of regional analyses and genetic controls

There is substantial brain development during adolescence, which continues up to the early 20s. One of the earliest questions in neuroscience has been the role of experiences, or environmental factors, in that development. As pointed out by Turkheimer[1], "development is fundamentally nonlinear, interactive, and difficult to control experimentally". But, in the last two decades, there has been an enormous progress in brain measurements, cognitive testing, and sample sizes.

Perhaps the most well-studied environmental factor in cognitive development is socioeconomic status (SES). This index is a combination of multiple factors that can impact the cognition of a child, such as the influence of parental education (e.g., the types of books in the household and the intellectual stimulation at the dining table); the influence of income in the quality of the school and the number of extra-curricular activities; the influence of the neighborhood in the type of peers and services available. Children born and raised to parents with low SES have on average a worse development in a wide range of areas: they tend to have lower cognitive abilities and worse academic performance, and to suffer more frequently from mental disorders[2,3].

It is not surprising then that functional magnetic resonance imaging (fMRI) studies show that the brain systems whose activity is affected by SES are frontal and parietal regions related to reasoning and executive functions, temporal language areas, as well as the hippocampus and the medial temporal lobe, which are related to long-term memory[4].

The neurological impact of SES goes even beyond task-specific brain activity at the moment of scanning (as measured by fMRI). SES is one of the few environmental variables that we know can impact the very macrostructure of the brain (as measured by structural MRI), such as cortical surface area, which is typically stable over months and even years of life. A large study imaging the brains of 1,099 individuals between the ages of 3 and 20 years found that the total cortical surface area was related to both parental income and parental educational level[5]. There were regional associations in most parts of the cortex, but in particular in regions supporting language, reading, executive functions, and spatial skills. Other studies have supported these findings, but some show that the frontal cortex is especially targeted, while others show no single region that is specifically connected to SES[4].

There are, however, some caveats that should be kept in mind when interpreting MRI results in this field. First, studies typically suffer from a methodological "blind spot", because global differences in the structural measures, for example in cortical surface area, are often not taken into account. It is therefore unclear if regional findings mean that low SES selectively impacts only specific brain areas or if the impact is better described as broad and global, with minor local variability. Second, SES is likely not to be an entirely environmental factor, but to have a substantial genetic component. For example, it has been reported[6] that a set of genetic markers explained as much as half of SES contributions to school achievement in 16-year-olds.

In a recent study[7], we used a sample of 551 typically developing adolescents, studied at ages 14 and 19, to try to tackle the problem of the entanglement between genetic and environmental effects in the developing brain. In order to estimate genetic effects, we used a combined measure, called polygenic score (PGS), from several thousand DNA markers that were selected and given a weight to optimize prediction of educational attainment (henceforth called EduYears-PGS). As expected, EduYears-PGS and SES were moderately correlated. But, even when controlling for this overlap, SES still had independent effects on cognitive ability at age 14. Interestingly, the SES effect was about twice as strong as that from EduYears-PGS. When analyzing the change in cortical surface area from age 14 to 19, there was an effect of SES, but not EduYears-PGS. This indicated that SES continued to affect brain maturation throughout adolescence.

One limitation of the study was that, although the EduYears-PGS measure is the most powerful genetic predictor available for educational attainment, it does not capture all the genetic variance associated with SES, as suggested by twin studies. Another limitation is that the EduYears-PGS was optimized to predict educational outcome, rather than SES. However, our *post-hoc* analysis suggested that the SES associations that we found were driven almost exclusively by differences in parental education and, as a control for that, the EduYears-PGS we used is optimal.

Regarding the methodological "blind spot" problem mentioned above, we also obtained structural MRI from the adolescents. Initially, we found that both EduYears-PGS and SES were positively correlated with total cortical surface area. However, after controlling for the global effects, there were no additional regional associations of SES to cortical surface area. This means that there were no signs of any particular structure or neural system being selectively affected above and beyond the broad effects of SES. The EduYears-PGS, on the other hand, had an additional regional association with cortical surface area in the right parietal lobe.

The association of SES to global cortical surface area means that the behavioral and psychological consequences of low SES are likely wide-ranging. What could be the environmental factors behind such a broad effect in the developing adolescent brain? Low SES is associated with a range of environmental factors that could impact cognition and brain development. These include toxins, infections and stress during gestation, inferior nutrition, chronic stress, and lack of cognitive stimulation during childhood and adolescence[8,9].

Because research typically shows that the impact of SES continues throughout adolescence, one could expect that the environmental factors during this period play an especially important role, such as chronic stress or lack of intellectual stimulation, rather than gestational factors. Furthermore, if these broad brain impacts (as suggested by regional analyses controlling for global

measure) are indeed true, this has negative implications for societies. It makes it less likely that any particular intervention, such as language training, could compensate for the cognitive and behavioral problems. An unfortunate implication of poverty.

However, it is possible that the global neural effect of low SES is the result of a combination of a multitude of environmental effects, and that each of these can be identified and targeted. Future research might thus highlight the role of specific environmental factors in affecting cognitive development, which could help inform policy decisions.

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The evolving epidemiology and differential etiopathogenesis of eating disorders: implications for prevention and treatment

Profound changes in the classification of eating disorders have occurred over the past decades. The expanded diagnostic spectrum of feeding and eating disorders now ranges from conditions characterized by food restriction (anorexia nervosa and avoidant/restrictive food intake disorder, ARFID) through to those typified by food craving and overeating (bulimia nervosa and binge eating disorder).

Since the advent of the DSM-5 in 2013, amenorrhea is no longer required to diagnose anorexia nervosa, and binge eating disorder is a fully recognized diagnostic entity. Most previous differences between the ICD and DSM have now been eliminated: the ICD-11 is broadly similar to the DSM-5, the only important difference being that subjective binges are accepted for an ICD-11 diagnosis of binge eating disorder.

About 1.4% of women and 0.2% of men experience anorexia nervosa during their lifetime; 1.9% of women and 0.6% of men are affected by bulimia nervosa, while 2.8% of women and 1.0% of men develop binge eating disorder. So, binge eating disorder is the most prevalent eating disorder[1].

To judge time trends in the occurrence of new cases, only longitudinal incidence studies on large population-representative samples can provide clarity. Incidence studies count new cases of eating disorders in dynamic populations, meaning that individuals can enter or leave the underlying population by, for example, immigrating to a country or dying. Therefore, each individual in the population is followed up for a different time period. These individual follow-up durations are summed to the total follow-up time expressed in person-years. New cases per person-year are measured by incidence rates.

Although diagnostic specifiers have evolved over time, the incidence of anorexia nervosa and bulimia nervosa presenting to primary care, in countries (such as the UK and the Netherlands) where this is an entry point for secondary care, has been relatively stable over the last six decades[2]. On the other hand, admissions for inpatient treatment for anorexia nervosa have rapidly increased in several European countries, despite most guidelines recommending this as a tertiary form of management. The explanation for this discrepancy in service use is uncertain. One possibility is that a reduced mortality rate has allowed those with a severe form of illness to survive for longer. Another possibility is that environmental protective factors may have decreased whilst perpetuating factors have increased.

There are many contrasts in the clinical features and underlying etiopathogenesis between anorexia nervosa and binge eating disorder. Anorexia nervosa has an earlier onset in the peripubertal period. In binge eating disorder, the female:male ratio is lower, the risk in ethnic minorities is higher, and a developmental and/or family history of higher weight is commonly present. As binge eating disorder is such a recent diagnosis, incidence studies with sufficient follow-up time have not yet been performed[2].

There are no genome-wide association studies on bulimia nervosa or binge eating disorder, but emerging work suggests that the genetic risk profile differs from that of anorexia nervosa. For example, a study using the UK Biobank cohort found that adults who engage in binge eating carry a polygenic liability to higher body mass index (BMI) and attention-deficit/hyperactivity disorder (ADHD)[3]. This contrasts to the negative genetic association with BMI and variables related to the metabolic syndrome in anorexia nervosa[4].

Over the past 70 years, the food environment has changed rapidly. Food technology has increased access to cheap, highly palatable foods (combining salt, sweet and fatty elements), refined for rapid absorption. This has contributed to changes in eating behaviour, such as the reduction in social eating and increase in fast food consumption. These changes in the food environment are likely to have contributed to an increased prevalence of binge eating.

Another key social determinant is weight stigma (social rejection, teasing, bullying and devaluation because of a bigger body), particularly if the body shaming induced is internalized. Weight stigma may be compounded by other forms of trauma, alienation and discrimination that may occur in marginalized groups.