INVITED SYMPOSIUM EARA 2018

Gene-Environment Interplay in Adolescence:

Gene-Environment Interactions and Methylation

Chair: Luc Goossens, University of Leuven, Belgium

Discussant: Luc Goossens, University of Leuven, Belgium

It is widely assumed that problem behaviors in adolescence emerge through some sort of interplay between genes and the social environment. The traditional approach to studying such interplay concentrates on variations in a single gene that interact with environmental factors. This approach ignores the fact that problem behaviors are determined by multiple genes and that gene functioning (i.e., the degree to which the genetic code can be transcribed easily) is also associated with these problematic behaviors. The present symposium focuses on alternative approaches that try to remedy these shortcomings of current research. Studies 1 and 2 used summary measures of genetic risk across multiple genes (so-called genetic risk scores). Study 1 showed that higher levels of parental support were associated with lower levels of externalizing problems, but only at lower levels of genetic risk for inadequate dopamine signaling. Study 2 showed that greater genetic risk for major depressive disorder (MDD) was associated with higher levels of depressive symptoms, but only at high levels of maladaptive parenting. Studies 3 and 4 examined links between methylation (i.e., a process that negatively affects gene functioning) and adolescent problem behavior. Increased methylation is thought to be linked to negative environmental conditions. Study 3 found prospective links between chronic victimization during childhood and increased methylation in two stress-related genes, on the one hand, and adolescent anxiety, on the other hand. Study 4 examined concurrent links between parenting, attachment, and increased methylation in several stress-related genes, on the one hand, and internalizing problems (i.e., depressive symptoms, loneliness, and social anxiety) during adolescence, on the other hand. Implications of these findings for our understanding of gene-environment interplay as it contributes, in its various forms, to the emergence of problem behaviors in adolescence are discussed.

PRESENTATION 1: Parenting, effortful control, and externalizing problem behavior: Moderation by dopaminergic genes

Martijn Van Heel, Patricia Bijttebier, Stephan Claes, Hilde Colpin, Luc Goossens, Wim Van Den Noortgate, Karine Verschueren, & Karla Van Leeuwen

University of Leuven, Belgium

Introduction. The literature has suggested that both higher parental support and effortful control are associated with lower levels of externalizing problem behavior (i.e., rule-breaking behavior and aggressive behavior). More recently, G x E studies showed that the association between externalizing problem behavior and environment is moderated by dopaminergic genes. The present study aimed to build on this finding by including dopamine, in addition to parental support (i.e., an environmental characteristic) and effortful control. More specifically, we examined (a) whether there are associations between parental support, effortful control, and externalizing problem behavior, and (b) whether dopaminergic genes moderate the aforementioned associations. *Methods.* In the present study, a community sample of 419 adolescents (Age: *M* = 16.87 years, range= [14.75; 19.73]) reported on their own effortful control and externalizing problem behavior as well as on parental support. Additionally, saliva samples were collected to gain information on their genetic characteristics. A Biologically Informed Multilocus Profile Score (BIMPS; Range= [0;4]) was computed to represent the genetic base of dopamine signaling across four dopamine polymorphisms (i.e., DAT1, DRD2, DRD4, and COMT; Nikolova et al., 2011). Based on these scores, the adolescents were allocated to a 'low' (0-1.5), 'intermediate' (2-2.5), or 'high' (3-4) group. *Results.* Multigroup structural equation modeling, separately for rule-breaking and aggressive behavior, revealed that higher parental support was associated with lower levels of both rule-breaking and aggressive behavior and higher levels of effortful control, but only in the 'low' and 'intermediate' dopamine signaling groups. There were also differences between rule-breaking and aggressive behavior. First, greater effortful control was associated with lower aggressive behavior, and this association was directly proportional to the level of dopamine signaling, whereas this association was only observed in the 'intermediate' group for rule-breaking behavior. Second, effortful control partially mediated the association between parental support and aggressive behavior in the low dopamine signaling group, whereas this mediation was only observed in the 'intermediate' group for rule-breaking behavior. In general, higher levels of parental support were positively associated with effortful control, which in turn was negatively associated with externalizing problem behavior. *Discussion.* Consistent with the literature our results suggest that higher parental support was associated with lower externalizing problem behavior. However, the genetic base of dopamine signaling appears to moderate this association, which is also consistent with suggestions in the literature that dopamine can moderate the association between externalizing problem behavior and environmental influences. It appears that adolescents with reduced dopamine signaling activity benefit most from parental support. Furthermore, the levels of dopamine signaling also seem to moderate the association between effortful control and externalizing problem behavior. This moderation differs between rule-breaking and aggressive behavior, which may suggest an etiological difference in the genetic characteristics of the adolescent.

PRESENTATION 2: Polygenic risk for MDD interacts with maladaptive parenting to predict adolescent depressive symptom development

Stefanie A. Nelemans, Bochao Lin, Susan J. T. Branje, Marco Boks,
Tineke Oldehinkel, Pol A. C. van Lier, & Wim H. J. Meeus
Utrecht University, the Netherlands

Adolescence is a critical phase for the development of depressive symptoms and research that focuses on the development of depressive symptoms in adolescence and identifies factors that affect this development is essential. Research is increasingly focused on identifying genetic underpinnings of psychopathological symptoms and disorders, including Major Depressive Disorder (MDD). This field of research has recently moved from investigating simple, single genetic markers (i.e., candidate genes) to more complex genetic indices that are based on multiple genes across the human genome (i.e., polygenic risk scores based on genome-wide association studies). Importantly, Hyde et al. (2016) recently published a crucial meta-analytical study identifying several genetic loci associated with risk of MDD in individuals of European descent, which represents an important breakthrough in the identification of the genetic underpinnings of MDD. However, still unknown to this moment is whether these genetic loci associated with heightened risk of MDD in adulthood are also associated with depressive symptom development from early to late adolescence. In addition, polygenic risk for MDD may interact with individual differences in environmental exposure in predicting adolescent depressive symptom development (G×E). Hence, the present study examined polygenic risk for MDD as well as interactions between polygenic risk for MDD and a multi-informant longitudinal index of maladaptive parenting in relation to adolescent depressive symptom development in a community sample followed from early to late adolescence. Our sample consisted of 327 adolescents (56% boys; M_{age} T_1 = 13.00). Adolescents reported on their depressive symptoms and both adolescents and their mothers reported on parental criticism for 6 successive years. Polygenic risk scores (PRSs) for MDD were created based on the recent Hyde et al. (2016) meta-analysis (p-values < 5×10^{-8}) and the 23andMe data (13 PRSs with different p-value thresholds, ranging from 5×10^{-8} to 0.05). Latent Growth Models were estimated to capture levels of adolescent depressive symptoms and change in these levels across adolescence, with MDD PRS and MDD PRS × parental criticism as predictors. Findings suggested that polygenic risk for MDD was robustly associated with higher levels of depressive symptoms across adolescence, particularly for adolescent girls, with some indications for associations with less developmental change (i.e., stronger stability) in depressive symptoms over time, again particularly for adolescent girls. Importantly, polygenic risk for MDD significantly interacted with maladaptive parenting in predicting depressive symptoms and development in symptoms across adolescence. Specifically, strong polygenic risk for MDD was associated with the highest depressive symptoms across adolescence at high levels of maladaptive parenting but not associated with depressive symptoms at low levels of maladaptive parenting (in line with the diathesis-stress framework). In contrast, weaker polygenic risk for MDD was associated with the highest depressive symptoms across adolescence at high levels of maladaptive parenting but also the lowest depressive symptoms across adolescence at low levels of maladaptive parenting (in line with the differential susceptibility framework). No sex differences were found in these G×E effects on adolescent depressive symptom development. Implications of these findings are discussed in the context of individual-by-environment models.

PRESENTATION 3: Impact of bullying-victimization on DNA methylation of stress-related genes and the development of anxiety: A longitudinal study from birth to adolescence

Marieke Buil, Charlotte Cecil & Ted Barker

Vrije Universiteit Amsterdam, the Netherlands

Background. Chronic bullying-victimization can have life-long effects on the development and well-being of affected children and adolescents and is associated with (later) psychopathology, most notably emotional problems such as anxiety. Emerging evidence emphasizes the importance of epigenetic mechanisms that regulate gene expression, including DNA methylation, as a potential etiological pathway explaining why these long-lasting effects might occur. The current study investigated whether DNA methylation patterns of two stress-related genes (the serotonin transporter gene; *SERT,* and the glucocorticoid receptor gene; *GR*) at birth, age 7 and age 15, were different for children who were chronically bullied during elementary school, versus children who were not chronically bullied. Furthermore, we investigated whether these potential DNA methylation differences coincided with increased anxiety levels from age 7 to age 15 years for victimized children compared to non-victimized children.

Method. Participants were 907 children (49% boys) followed annually from birth until age 15 years. These children were part of the Avon Longitudinal Study of Parents and Children (ALSPAC). Children reported on victimization (Bullying and Friendship Interview Schedule; Wolke et al., 2000) at ages 8, 10 and 12 years. *SERT* and *GR* methylation levels were retrieved from cord blood samples at birth and peripheral blood at ages 7 and 15. Parent-reports (age 7) and self-reports (age 15) were used to assess symptoms of generalized anxiety disorder (Development and Wellbeing Assessment, DAWBA; Meltzer et al., 2000).

Results. Results from latent profiles analyses indicated that 62 (7%) of our sample was chronically bullied during the elementary school years and 845 (93%) was not chronically bullied. Furthermore, no differences were found between victims' and non-victims' DNA methylation levels at birth. However, from age 7 onwards, chronically victimized children had heightened DNA methylation levels of both *SERT* and *GR,* compared to non-victimized children. DNA methylation differences were most pronounced at age 15 years. Preliminary analyses indicate that these heightened methylation patterns for victimized children coincide with increasing anxiety levels from age 7 to 15 in these children, while non-victimized children showed no increases in DNA methylation or anxiety.

Conclusion. Our results imply that children's experience of chronic bullying-victimization during elementary school may alter epigenetic regulation of two key stress-related gene over time. This indicates that DNA methylation of *SER*T and *GR* might be an important pathogen explaining the link between bullying-victimization and the development of anxiety in adolescence.

PRESENTATION 4: Internalizing problems in adolescence:

Methylation across time and links with stress reactivity and information processing

Flore Geukens, Magali Van de Walle, Filip Calders, Viktoriia Chubar, Tanya Van Aswegen,
Sofie Weyn, Patricia Bijttebier, Karla Van Leeuwen, Wim Van den Noortgate,
Stephan Claes, Guy Bosmans, & Luc Goossens
University of Leuven, Belgium

Methylation is a process that makes it harder for the body to read or transcribe the information contained in the genetic code, thus leading to impaired gene functioning. Gene methylation is typically thought to represent a mechanism that links early life stress as a result of maltreatment to poor psychological functioning in later life. However, recent research suggests that concurrent life events, as experienced during adolescence, are a better predictor of adolescents' methylation levels than negative life events experienced at an earlier age. This finding raises questions about the temporal stability of methylation across time and about the underlying mechanisms that link methylation to problem behaviors.

The Methylation in Development (MIND) project aims to answer all these questions, by providing a comprehensive picture of the role that methylation plays in the development of internalizing problems (i.e., depressive symptoms, loneliness, and social anxiety) in adolescence. A large group of young adolescents (*N* = 600; 10 years of age) will provide a saliva sample and complete measures of perceived parenting, attachment, and internalizing problems at three waves with a one-year interval. At Wave 2, a subgroup will be given an objective stress task (i.e., the Trier Social Stress Test for Children; TSST-C) and a computer-administered information processing task.

Three issues will be addressed. First, maladaptive parenting and insecure attachment will be related to the degree of methylation in the promotor region of several genes that are linked to the stress system, for instance, the glucocorticoid receptor gene (NR3C1), the serotonin receptor gene (SLC6A4), and the oxytocin receptor gene (OXTR), at Wave 1. Methylation, in turn, will be related concurrently to the level of internalizing problems. Second, correlations among the methylation levels at the three waves will be examined to study the neglected topic of methylation stability over time (Waves 1 to 3). In addition, changes in methylation levels across time will be related to changes in internalizing problems across the same time interval. Third, stress reactivity and biased information processing will be examined as potential intermediate processes between gene methylation (presumably associated with negative environmental conditions), on the one hand, and internalizing problem behaviors, on the other hand. Specifically, methylation levels in the stress-related genes will be related to stress reactivity as observed in cortisol changes during the objective stress task (TSST-C) and speed and accuracy when processing emotionally charged information in a computer-administered task. Preliminary findings, based on Wave 1, will be presented at the symposium and their implications for current understanding of internalizing problems in adolescence will be discussed.