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GENETIC AND ENVIRONMENTAL INFLUENCES ON MAJOR DEPRESSION IN YOUTH

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Piechaczek CE, Greimel E, Feldmann L, Pehl V, Allgaier A-K, Frey M, Freisleder FJ, Halldorsdottir T, Binder EB, Ising M, Schulte-Körne G. Interactions between *FKBP5* variation and environmental stressors in adolescent Major Depression. *Psychoneuroendocrinology*. 2019; 106: 28-37. doi: 10.1016/j.psyneuen.2019.03.025.

Halldorsdottir T, **Piechaczek** C, de Matos APS, Czamara D, Pehl V, Wagenbüchler P, Feldmann L, Quickenstedt-Reinhardt P, Allgaier A-K, Freisleder FJ, Greimel E, Kvist T, Lahti J, Räikkönen K, Rex-Haffner M, Örn Arnarson E, Craighead E, Schulte-Körne G, Binder EB. Polygenic risk: predicting depression outcomes in clinical and epidemiological cohorts of youths. *Am J Psychiatry*. 2019; 176: 615-625. doi: 10.1176/appi.ajp.2019.18091014.

Summary

Major Depression (MD) is a common and debilitating psychiatric disorder, affecting about 7.5% of adolescents. The disorder is associated with many adverse consequences, such as impairments in interpersonal relationships, difficulties at school, and heightened suicide risk. The factors contributing to the complex etiology of MD are manifold. Of note is that traumatic experiences like maltreatment during especially vulnerable developmental periods, such as youth, are potent risk and maintaining factors contributing to MD. In addition, psychosocial stressors which are prevalent in everyday life, such as those occurring at school and in family and peer contexts, are supposed to play an important role in the development of MD. It is also known that sociodemographic stressors (e.g., low education level of parents) contribute to the development of MD during youth. Due to the significance of traumatic experiences and psychosocial stressors, MD can be described as being stress-related. Next to psychosocial adversity, genetic factors are also important influencing factors and interact with psychosocial stressors and traumatic experiences, heightening the risk of MD. For a better understanding of the factors contributing to MD, the present dissertation investigates the role of (a) psychosocial adversity differing in type and severity, (b) genetic factors, as well as (c) the interplay between these sources of risk, in the context of MD during youth. Publication I focuses on clinically depressed adolescents and typically developing peers. It addresses the interplay between qualitatively distinct psychosocial stressors and variation in *FKBP5*, a gene implicated in the physiological stress response. Results indicate interactions between genetic variation in *FKBP5* (i.e., single nucleotide polymorphisms/SNPs, and the CATT haplotype consisting of minor alleles of several *FKBP5* SNPs) and different psychosocial stressors. In more detail, the probability for being diagnosed with MD increased depending on the number of moderate and sociodemographic stressors, as well as the total number of stressors experienced. This relationship was stronger in adolescents carrying at least one minor allele of different *FKBP5* SNPS/at least one copy of the CATT haplotype.

Publication II addresses the role of polygenic risk scores (PRS) for depression, as well as experiences of maltreatment. It could be shown that youths with heightened PRS and more incidences of maltreatment had a higher probability of being diagnosed with MD. Furthermore, higher PRS were associated with a younger age of onset and were also related to a higher level of depressive symptoms in conjunction with the experience of maltreatment in depressed patients. In an additional juvenile epidemiological sample, positive cross-sectional and prospective longitudinal associations were found between PRS and maltreatment, and heightened depressive symptoms.

Results from the two publications underline the importance of genetic factors and adverse psychosocial experiences, as well as their interplay, in the context of youth MD and depressive symptoms. Following these results, important starting-points for efforts aiming at early identification, prevention, and treatment approaches can be deduced. In more detail, the publications clearly emphasize the relevance of different types and severities of psychosocial adversity contributing to MD. This knowledge can play an important role in early identification and subsequent preventive efforts. Furthermore, in the long-run, PRS may have important implications for identifying youths at high risk of MD. Of note, knowledge on genetic factors may ultimately guide treatment efforts; for instance, PRS may be included in diagnostics, treatment planning, as well as in the prevention of relapse and recurrence. Additionally, *FKBP5* might be an interesting target for the effects of antidepressant agents. Above all, implementing the combination of different sources of risk, i.e., genetic information as well as psychosocial adversity, in identification, prevention, and treatment approaches in the context of MD during youth might be particularly fruitful. Next to focusing on risk factors for MD, expanding these analyses to protective factors might also offer important future insights with regard to clinical applications.

Deutsche Zusammenfassung

Die Depression ist eine häufig vorkommende psychiatrische Erkrankung, die circa 7,5% der Jugendlichen betrifft. Die Erkrankung steht in Zusammenhang mit negativen Konsequenzen, wie Beeinträchtigungen in zwischenmenschlichen Beziehungen, Schwierigkeiten in der Schule sowie einem erhöhten Suizidrisiko. Die Faktoren, die einen Einfluss auf die komplexe Ätiologie der Depression haben, sind mannigfaltig. Vor allem traumatische Erlebnisse (z.B. Misshandlungserfahrungen) während besonders sensibler Entwicklungsperioden, wie der Kindheit und Jugend, stellen wichtige Risikofaktoren dar und tragen zu einer Aufrechterhaltung der Depression bei. Darüber hinaus gelten alltägliche psychosoziale Stressoren, u.a. Probleme in der Schule oder im Familien- und Peerkontext als wichtige Faktoren in der Ätiologie der Depression im Kindes- und Jugendalter. Auch soziodemografische Stressoren (z.B. Bildungsgrad der Eltern) können eine wichtige Rolle in der Entstehung der Depression im Kindes- und Jugendalter einnehmen. Aufgrund der Relevanz traumatischer Erlebnisse sowie psychosozialer Stressoren gilt die Depression als stressbedingt. Neben psychosozialen Belastungsfaktoren spielen auch genetische Faktoren sowie das Zusammenspiel dieser Faktoren eine bedeutende Rolle bei der Entstehung einer Depression und tragen zu einem erhöhten Depressionsrisiko bei. Um die Faktoren besser verstehen zu können, die einen Einfluss auf die Entwicklung einer Depression nehmen, wird in der vorliegenden Dissertation die Bedeutung (a) psychosozialer Belastungsfaktoren unterschiedlichen Typs und Schweregrads, (b) genetischer Faktoren sowie (c) des Zusammenspiels zwischen diesen Faktoren im Kontext der Depression untersucht.

Der Fokus von Publikation I liegt auf klinisch depressiven sowie gesunden Jugendlichen. Diese Publikation adressiert das Zusammenspiel zwischen qualitativ unterschiedlichen psychosozialen Stressoren und Variation im *FKBP5*-Gen, das eine wichtige Rolle in der Regulation der physiologischen Stressreaktivität spielt. Es zeigten sich Interaktionen zwischen Variation im *FKBP5*-Gen (Einzelnukleotidpolymorphismen/*single nucleotide polymorphisms*/SNPs sowie der CATT-Haplotyp bestehend als minoren Allelen unterschiedlicher *FKBP5* SNPs) und unterschiedlichen psychosozialen Stressoren. Jugendliche, die eine erhöhte Anzahl moderater und soziodemografischer Stressoren sowie eine erhöhte totale Anzahl an Stressoren erlebt hatten, wiesen eine erhöhte Wahrscheinlichkeit auf, die Diagnose Depression erhalten zu haben. Diese Wahrscheinlichkeit war am höchsten bei denjenigen Jugendlichen, die mindestens ein minores Allel unterschiedlicher *FKBP5* SNPs bzw. mindestens eine Kopie des CATT-Haplotypen trugen.

Publikation II adressiert die Bedeutung von polygenen Risikowerten für Depression (*polygenic risk scores*, PRS) sowie Misshandlungserfahrungen. Es konnte gezeigt werden, dass Kinder und Jugendliche mit der Diagnose einer Depression höhere PRS aufwiesen und häu-

figer Misshandlungserfahrungen ausgesetzt waren als gesunde Altersgenossen. Zudem wurde ein Zusammenhang gefunden zwischen erhöhten PRS und einem jüngeren Ersterkrankungsalter. Es zeigte sich außerdem ein Zusammenhang zwischen PRS bzw. Misshandlungserfahrungen und einer schwereren depressiven Symptomatik bei depressiven Patienten. In einer epidemiologischen Stichprobe bestehend aus Jugendlichen konnten sowohl querschnittliche als auch prospektive positive Zusammenhänge zwischen PRS, Misshandlungserfahrungen sowie erhöhten depressiven Symptomen gefunden werden.

Die Ergebnisse der Publikationen unterstreichen die Bedeutung genetischer Faktoren und psychosozialer Belastungsfaktoren sowie ihres Zusammenspiels im Kontext der Depression im Kindes- und Jugendalter. Die Publikationen zeigen eine Reihe von Anknüpfungspunkten auf für frühe Maßnahmen zur Identifikation, Prävention sowie Behandlung der Depression im Kindes- und Jugendalter. So heben Publikation I und II deutlich die Relevanz psychosozialer Stressoren unterschiedlichen Typs und Schweregrads hervor. Diese Erkenntnisse bieten wichtige Ansatzpunkte für die Identifikation von Kindern und Jugendlichen mit einem erhöhten Risiko für eine Depression und nachfolgenden präventiven Maßnahmen. PRS könnten längerfristig eine wesentliche Bedeutung einnehmen bei der Identifikation von Kindern und Jugendlichen, die ein erhöhtes Risiko für die Entwicklung einer Depression haben. Darüber hinaus könnte ein verbessertes Wissen bezüglich genetischer Risikofaktoren langfristig einen wichtigen Beitrag zur Therapie der Depression im Kindes- und Jugendalter liefern; beispielsweise wäre es denkbar, PRS in Diagnostik, Planung von Behandlungen oder in die Prävention von Rückfällen und Rezidiven einzubeziehen. Das *FKBP5*-Gen könnte zudem ein interessantes Ziel für antidepressive Medikation darstellen. Insbesondere die gleichzeitige Einbeziehung unterschiedlicher Risiko- und Belastungsfaktoren, wie genetische Informationen und psychosoziale Stressoren, in Ansätzen zur Identifikation, Prävention und Behandlung der Depression im Kindes- und Jugendalter erscheint vielversprechend. In Hinblick auf klinische Anwendungsbereiche wäre es bedeutsam, in zukünftigen Studien neben Risikofaktoren für die Depression auch protektive Faktoren zu betrachten.

Introduction to the cumulative dissertation

The burden of major depression in youth

Major Depression (MD) is a prevalent psychiatric disorder with more than 300 million individuals being affected worldwide.[1] While MD can occur at any time during the life span, prevalence rates are relatively low during childhood, but markedly rise thereafter, with at least 7.5% of adolescents suffering from the disorder.[2,3] Youth MD is associated with a reduced functioning in school, peer and family contexts and a heightened risk of suicide.[2-5] Moreover, MD during youth is characterized by a heightened rate of recurrence and an increased risk of chronification, as well as difficulties related to work, social and academic contexts that can persist into adulthood.[4] Relatedly, subsyndromal depressive symptoms, which represent a major risk factor of developing MD, are a prevalent phenomenon with 8.2% of youths reporting elevated depressive symptoms.[6,7] It is notable that suffering from heightened depressive symptoms during youth is associated with, e.g., impairment affecting the individual's school career and negative effects in adulthood, including difficulties in interpersonal relationships and lower levels of education and income.[7-9] For these reasons, MD during youth represents a significant challenge for the society and healthcare system, as well as for science.

Although effective approaches for preventing and treating MD do exist, their effects are usually small or not more than moderate.[10-13] This can in part be attributed to the etiological complexity of MD, as well as to the fact that contributing factors are still not sufficiently understood. These factors include the biological underpinnings of the disorder, e.g., genetic factors, as well as their interplay with psychosocial factors. Notwithstanding, progress has been made in advancing knowledge of biological aspects contributing to the development and maintenance of MD, e.g., by identifying genetic and epigenetic factors.[14,15] In the same vein, the importance of psychosocial adversity in the context of MD seems indisputable.[16] It is therefore crucial to come to a better understanding of the biological and psychosocial factors contributing to MD in youth and of their interplay, in order to increase efforts aiming at (a) the identification of youths with high risk, and (b) related preventive efforts, as well as (c) the further development of treatment options.[14]

Developmental processes during youth

The developmental period of youth is characterized by normative changes in biological systems, such as the maturation of the hypothalamic-pituitary-adrenal (HPA)-axis, which represents a major stress system.[17,18] During puberty individuals experience a rise in the

amount of stress, especially occurring in the psychosocial environment. In addition, youths tend to show a heightened emotional responsivity towards these stressors and do not own fully elaborated strategies to avoid or counteract stress.[18-20] These factors render youths vulnerable to developing MD and contribute to the increase in prevalence rates.[18-20] Of note, youth can be regarded as a particular sensitive and plastic developmental period.[21,22] That is, youths are especially receptive to experiences, so that adversity during this time can have profound and long-lasting effects on developing stress systems, such as the HPA-axis.[17,21] The repeated experience of stress over a prolonged period of time can have a wide range of adverse effects on health, including an increased risk of psychiatric disorder like MD.[17] MD during youth is associated with intensive personal suffering and can have detrimental effects on the current and future development. Therefore, it seems especially relevant and promising with regard to identification, prevention and treatment efforts to identify factors contributing to MD during this developmental period.[2-5]

Psychosocial and genetic factors contributing to major depression

MD is a complex psychiatric disorder with many interrelated biological, psychosocial and cognitive factors being implicated.[3] As adversity in the (psychosocial) environment often precipitates MD, it can be conceptualized as being stress-related.[23-25] Previous research has shown that early traumatic experiences, such as physical maltreatment or sexual abuse, have a strong effect on the development of MD.[26] Additionally, also relatively common and less severe psychosocial stressors, which are part of everyday life, including conflict with parents and peers or problems at school, represent important factors contributing to the disorder.[3,27,28] In addition, it has been demonstrated that sociodemographic characteristics of the family, such as a low academic qualification of the parents, are linked to MD via its associations with heightened levels of other (psychosocial) stressors.[29] The frequent and intense experience of stress can lead to a dysregulation of the HPA-axis, which may predispose youths towards developing MD.[17] Consequently, a large number of juvenile patients suffering from MD show elevated levels of cortisol, reflecting functional alterations of the HPA-axis.[30]

Next to psychosocial adversity, it is known that MD has a genetic component.[3] These genetic factors explain about 40% of the variation in MD during adolescence.[31] In addition to family/twin studies aiming at estimating the genetic and environmental proportions contributing to MD, different approaches exist, which address molecular genetic factors. The candidate-gene approach, for instance, focuses on the identification of variation in specific genes likely implicated in MD.[32] This approach is guided by existing theories on the biolog-

ical bases of MD. It often focuses on investigating single nucleotide polymorphisms (SNPs), which are common changes in single bases of the DNA.[32,33] For instance, knowledge of the depletion of monoaminergic neurotransmitters, such as serotonin, in depressed patients has inspired researchers to investigate genetic variation underlying putative mechanisms, e.g. by examining genetic variants in the gene coding for the serotonin transporter (*SLC6A4*).[34,35] Further well-studied candidate genes are those coding for other proteins related to monoaminergic neurotransmission, such as dopamine receptors or the dopamine transporter (e.g., *DRD2, SLC6A3*).[36,37] Other frequently studied candidate-genes are those coding for proteins being involved in the regulation of the HPA-axis, including FKBP51 (i.e., the *FKBP5*-gene).[38,39]

FKBP5 is a well-studied gene and is implicated in the physiological stress response.[40] Following an acute stressor, the HPA-axis is being activated and releases, amongst other peptides, glucocorticoids, including cortisol. Cortisol, in turn, binds to the glucocorticoid receptor (GR), which initiates a negative feedback loop with the goal of terminating the physiological stress response.[41] The activation of the GR is related to an increased transcription of *FKBP5* with associated heightened FKBP51 levels.[42,43] FKBP51, in turn, binds to the GR, inhibiting the suppression of the HPA-axis. This results in a subsequent prolonged physiological stress response, as reflected by, e.g., heightened levels of cortisol.[44,45] Genetic variation in *FKBP5* has been extensively studied in the realm of HPA-axis (dys-)regulation, the (psychosocial) reactivity towards stress, antidepressant treatment response, emotion regulation, and interactions with traumatic and stressful life events in the context of stress-related disorders, including MD.[46-51]

While the candidate-gene approach is strictly theory-driven, investigating variation in a single gene cannot accommodate the conceptualization of MD as a polygenic disorder arising from variation in many genes.[32,52] In line, recent investigations of the genetic bases of MD have focused on conducting genome-wide association studies (GWAS).[53-55] GWASs focus on SNPs and follow a theory-free, data-driven approach in which frequencies of alleles across the genome are compared between affected (e.g., those with depression) and healthy individuals.[54] Resulting identified alleles can then be used to calculate polygenic risk scores (PRS). PRS are thought to capture genetic variance in many genes with small effect sizes each and higher PRS reflect an increased genetic liability to the phenotype studied in the GWAS, e.g., depression.[54]

Gene-environment interactions in major depression

While MD has a genetic basis, genetic contributions to MD are small to moderate and other factors, such as psychosocial adversity considerably contribute to the disorder.[56,57] It needs to be noted, however, that not all individuals experiencing psychosocial stressors or even traumatic experiences develop MD. Likewise, a genetic vulnerability to MD, e.g., reflected in heightened PRS, does not necessarily lead to the disorder. These findings point to the notion that genetic factors and environmental stressors may interplay, a concept known as gene-environment interactions (G×E) as derived from the diathesis-stress model.[58-60] In particular, psychosocial adversity can modulate the relationship between genetic risk and MD, and vice versa.[22,59] Following the diathesis-stress model, genetic risk and adverse psychosocial experiences need to come together in order to contribute to an increase of the likelihood of developing MD.[58,60] In more detail, genetic factors can provide the diathesis to which different forms and intensities of adverse experiences can add up. When stressors of a certain intensity add to the diathesis, they will likely cross a critical point in the model, which facilitates the development of MD.[58,60]

Investigating different types and grades of severity of psychosocial adversity and genetic factors implicated in MD, as well as their interplay, cannot only contribute to a better understanding of possible mechanisms, which convey heightened risk of the disorder. This approach also offers the possibility for informing efforts for the identification, prevention and treatment of MD. First, knowledge about psychosocial adversity can help identifying youths at risk of developing MD. Second, many adverse psychosocial experiences can be prevented and the (emotional) reactions to them are often amenable to change. This offers starting-points for early preventive efforts and provides possible targets for treatment, e.g., cognitive-behavioral interventions. Third, with increasing insights on genetic factors contributing to MD, it is conceivable that this knowledge might help to identify youths with a heightened genetic risk for MD in the long-run. This, in turn, might be beneficial for early preventive and diagnostic efforts. Fourth, knowledge on genetic risk factors for MD may also have implications for treatment, e.g., by identifying youths at high risk of non-response or relapse following (pharmacological) treatment or by aiding in psychopharmacological treatment selection.[61] Fifth, the joint analysis of psychosocial adversity and genetic factors may be especially worthwhile since MD results from a complex interplay of different genetic, as well as other (e.g., psychosocial) factors. Combining information from several potential sources contributing to MD will likely be more beneficial than relying on one field of risk alone, especially with regard to early identification and prevention, as well as treatment efforts.[62]

Aim and results of the two studies

The objective of the two studies was to examine genetic factors and psychosocial adversity, as well as their interplay, in youth MD.[57,63] The two investigations follow different approaches regarding the conceptualization of (a) the genetic diathesis and (b) psychosocial adversity. Importantly, they include children and adolescents and thereby cover especially sensitive developmental periods.[21,22] In addition to the focus on MD, one of the studies additionally addresses (subsyndromal) depressive symptoms, thereby including two important aspects of the broader spectrum of depression. Together, the two studies complement each other by targeting different facets of the research question of how genetic factors, psychosocial adversity and their interplay contribute to MD in youth.

Publication I[63] focuses on variation in the *FKBP5*-gene and different types and severities of psychosocial stressors in adolescents diagnosed with a current episode of MD, as well as healthy peers. Five *FKBP5* SNPs, as well as the CATT haplotype (consisting of the minor alleles of four of these SNPs), were selected to investigate the genetic diathesis. To examine psychosocial adversity, a broad range of qualitatively distinct psychosocial stressors, which are particularly relevant during adolescence, were assessed (e.g., difficulties at school or in the peer context). These individual stressors were judged by the adolescents with respect to their perceived stressfulness. This approach allowed a classification of the individual stressors as mild, moderate or severe. Moreover, sociodemographic stressors were assessed on the basis of parental-report and are thought to reflect a more stable background condition of psychosocial adversity. Additionally, in order to depict a total measure of stressors experienced, a sum score was created by adding all individual mild, moderate, severe, and sociodemographic stressors. The main analyses of the study focused on interactions between *FKBP5* SNPs/the CATT haplotype and the different psychosocial stressors. Interactions were found between different SNPs/the CATT haplotype and moderate and sociodemographic stressors, as well as the total number of stressors experienced. The probability for being diagnosed with MD rose depending on an increasing number of moderate and sociodemographic stressors, as well as a growing number of total stressors experienced, respectively. This relationship was stronger in adolescents who carried at least one minor allele/one copy of the CATT haplotype, as compared with adolescents who were homozygous for the major allele/did not carry a copy of the CATT haplotype.

In **Publication II**[57] PRS, experiences of maltreatment, as well as their interactions were tested in a clinical sample of youths with a diagnosis of MD, and in a control group consisting of youths who were free of current and past psychiatric disorders. Results showed a

relationship between PRS and case-control status, i.e., youths with a higher PRS had a higher probability of being diagnosed with MD. Furthermore, in youths with MD, there was an association between PRS and age of onset, and severity of the depressive symptomatology, respectively. In more detail, a higher PRS was linked to a younger age of onset and a heightened level of depressive symptoms. In addition, additive effects of PRS and experiences of maltreatment were found. That is, heightened PRS and a higher incidence of maltreatment were both related to a heightened probability of being diagnosed with MD and a more severe depressive symptomatology. Furthermore, in this study, a juvenile epidemiological cohort was investigated. In this sample, a positive cross-sectional relationship was found between PRS and depressive symptoms. This association could be replicated in a community sample consisting of children, which was also investigated in this study. Interestingly, in the epidemiological sample, youths who did not show evidence of heightened depressive symptoms at the first point of measurement, but had moderate to severe depressive symptoms two years later, had higher PRS than individuals with no or mild symptoms. Additive effects of the PRS and experiences of maltreatment were found cross-sectionally, as well as in the prospective longitudinal analyses.

Discussion of the two publications and future prospects

By addressing different genetic factors and psychosocial adversities contributing to MD during youth, the two publications add to and advance knowledge of the complex etiology of MD during this sensitive developmental period. Therefore, important starting-points for (a) an early identification of individuals with a heightened risk of MD with subsequent preventive efforts, and (b) treatment can be deduced from the present findings.

First, results from both studies shed light on the relevance of different types and grades of severity of psychosocial adversity in the context of youth MD. It could be shown that traumatic experiences, such as maltreatment as well as more common and less severe psychosocial stressors (e.g., arguments with parents), substantially influence the development of MD and represent potent sources of risk. Moreover, as shown previously, these factors substantially contribute to the development of MD.[31,56] Hence, identifying youths who experience a great amount of different psychosocial stressors and those who even experience(d) traumatic life events would be an important first step towards identification and early prevention efforts. Importantly, Publication I addresses sociodemographic stressors. These factors are an important source of risk as they are assumed to not only reflect a considerable burden on their own. In line, it is known that they also convey a heightened risk of MD through their association with other stressors.[29] Sociodemographic stressors, such as the

academic qualification of the parents, cannot easily be addressed based on early interventions. Therefore, it is important to especially target youths who experience an elevated number of sociodemographic stressors when trying to prevent MD. This could be achieved, e.g., by approaching youths from lower sociodemographic backgrounds via schools. An additional benefit may be reached by identifying highly stressed youths who have parents who suffer from MD, as this is a highly potent (environmentally and genetically mediated) risk factor of MD.[64]

Second, while genotypic vulnerability is fixed, potential adverse effects of psychosocial adversity can be buffered in order to prevent the development of MD. As adversity during youth can have unfavorable consequences for well-being and mental health, it is important to consider that youth is also a sensitive period in which effective interventions can have especially favorable effects on future development.[21,65] For instance, emotional reactions to mild to moderate daily stressors (e.g., quarreling with parents) are not static, but can be modified. Therefore, for instance, youths could first be identified, who experience a heightened level of controllable daily stressors. Teaching them how to cope with these stressors through emotion regulation might be a worthwhile endeavor to avoid or reduce the negative emotional consequences of stress and to contribute to an increase in well-being and mental health.[66] In this vein, one possibility would be to teach youths to cope by means of cognitive reappraisal, i.e. they can be trained in generating more positive interpretations of negative experiences with the aim of ameliorating negative affect.[67] Moreover, severe adverse psychosocial experiences, such as maltreatment, especially when occurring very early during development, represent potent risk factors for MD and their negative (physiological) effects are usually long-lasting.[26] Since effective strategies for preventing childhood maltreatment are available, those efforts should be promoted in order to contribute to the prevention of MD. These approaches often consist of parental education with the aim of enhancing positive parenting behavior and providing information about child development.[68,69] Intense home visitations as early as during the prenatal period until infancy seem especially promising for the reduction of child maltreatment, particularly when high-risk populations are targeted (e.g., very young parents, single mothers or families with a low socio-economic background).[70]

Third, PRS might offer the chance for the identification of youth at high risk of MD. Publication II has shown that PRS for depression differ between youths with MD and their typically developing peers and can predict subsyndromal depressive symptoms over time. It also became evident, however, that PRS of depressed and healthy youths overlap substantially. Likewise, mean group values of PRS between youths with MD and their healthy counter-

parts, as well as between youths from the community with low vs. high depressive symptoms differ only slightly from each other.[71] Therefore, while PRS reflect genetic liability towards MD and subsyndromal depressive symptoms, they can currently not be used for predicting individual risk.[62,71] Notably, the PRS used in Publication II were derived from a large GWAS including adults.[55] Publication II could demonstrate that these PRS are also associated with clinical characteristics of MD in a sample of youths. In spite of that, it needs to be emphasized that the original GWAS, on which the PRS were based, focused on a broader spectrum of depression and did not exclusively rely on case-control samples consisting of clinically ascertained MD cases. Additionally, prospective predictions of the PRS in Publication II were restricted to the epidemiological sample and it was not explicitly studied whether heightened PRS might also predict future incidences of MD. Consequently, these issues could be important starting-points for future investigations examining the prediction of a full-blown episode via PRS in a sample of youths. Furthermore, there are indications showing that PRS do not seem to be specific for the disorder studied in the respective GWAS.[72] Thus, it would be important to investigate in future studies in what way specific PRS relate to distinct psychiatric disorders or to establish associations between PRS and distinct constellations of symptoms or intermediate phenotypes.[73] Despite these limitations, PRS for depression is a highly promising target with regard to clinical applications. It is conceivable that they can contribute to an improved identification of individuals with a high genetic risk of MD that may add to clinical information, such as a family history of MD in the future.[62,71,73]

Fourth, advanced knowledge on genetic factors contributing to MD might play an important role for the treatment of the disorder. As shown in Publication II, the genetic contribution to MD seems to be higher in more severely affected youths, as reflected in a positive relationship between PRS and heightened depressive symptoms. There are indications showing that an earlier age of onset represents a more severe form of MD.[4] Offspring from parents with an affective disorder tend to have a younger age of onset than those without affected parents.[74,75] This likely reflects heightened genetic risk of the disorder, which is in line with the finding in Publication II demonstrating a relationship between PRS and a younger age of onset. These insights concerning the contribution of molecular genetic factors to the severity of MD might play an important role in the planning of treatment, as well as relapse and recurrence prevention after treatment has ended. It is known that a more serious course of MD is associated with less favorable outcomes.[4] In line, knowledge about heightened genetic liability towards MD, which apparently reflects more severe forms of the disorder, can sensitize clinical practitioners, as well as depressed patients and their families to

take action for relapse and recurrence prevention and early treatment when depressive symptoms recur.

Moreover, since the candidate gene approach derives its target genes from theoretical models of the underlying biological mechanisms supposed to govern MD, these studies offer an important starting-point for a better understanding of the mechanisms of antidepressant agents.[76] For instance, it could be shown that antidepressant medications influence *FKBP5* expression and that this association is especially strong in minor allele carriers.[77] Furthermore, adult *FKBP5* minor allele carriers show a faster response to antidepressant medication.[46] It is conceivable that molecular genetic information in concert with other information, such as clinical characteristics, might aid guiding pharmacological treatment selection for individual patients in the long run.[78]

Fifth, as has been shown by Publication II, combining PRS and psychosocial adversity could increase the variance explained in clinical characteristics of MD and subsyndromal depressive symptoms. Therefore, it would be especially promising to make use of more than one risk source for ameliorating early identification, prevention, and treatment efforts.[62,71] Until now, genetic risk of MD is commonly inferred from a positive family history of an affective disorder. It needs to be proven if PRS in combination with information on familial history, as well as psychosocial adversity might improve predictive accuracy with regard to the development of MD.[73] This knowledge could then be used to enhance early identification, prevention, diagnostic and treatment approaches. It is important to consider that the genetic basis of MD is complex. Next to SNPs, also less common genetic variation, such as copy number variants (CNVs) might contribute to MD risk.[14] In addition, epigenetic changes, such as differing methylation levels, are likewise not captured by PRS, but also convey heightened vulnerability for the disorder.[15]

It would therefore be worthwhile in future studies to examine the role of epigenetic changes in the context of juvenile MD. Since these changes are not fixed, but highly sensitive to the environment, e.g., to psychosocial adversity, these factors also offer an important window for preventive and treatment options.[79] Likewise, by investigating the relationship between MD and stress more closely, it would be fruitful to focus on the association between genetic factors, psychosocial adversity, as well as potential intermediate phenotypes of MD, such as structural and functional brain changes and endocrine markers of stress, such as cortisol levels.[40,80,81] In the light of efforts aiming at identifying, preventing, and treating MD, it would also be highly important to gain more insight into the complex interplay between potential risk and protective factors. In contrast to the diathesis-stress model, the differential susceptibility model points out that carrying a certain diathesis (e.g., minor

FKBP5 SNPs or heightened PRS) might lead to a negative outcome when adversity is high. Likewise, when confronted with a positive, nurturing and supportive environment, individuals who have a heightened diathesis for MD might fare better than individuals without such a diathesis who experience a comparable positive environment.[82] This is also in agreement with the conceptualization of youth as a particular plastic and sensitive developmental period, with environmental experiences having the potential to lead to negative and positive outcomes, respectively.[21,22]

Own contribution to the publications

Data from this dissertation originate from two studies. The study "Molekulargenetik affektiver Störungen im Kindes- und Jugendalter" ("Molecular genetics of affective disorders during childhood and adolescence") was initiated in 2009. Funding by the "Randebrock Stiftung" was acquired by Prof. Dr. Gerd Schulte-Körne and Prof. Dr. Franz Joseph Freisleder. Positive ethical decisions by the Ludwig-Maximilians-University Medical Division Ethics Committee, Munich, Germany (study ID: 297-09) were granted for the initiation of the study and later amendments on 16/09/2009, 16/05/2012, and 13/05/2016, respectively. The first participant was included in 10/2009 and the study is currently ongoing. Data from participants taking part in this study were included in Publication I and II. Data were also gathered in the context of the research network "OptiMD", which has been funded by the "Bundesministerium für Bildung und Forschung" ("German federal ministry of education and research", project number 01EE1401D) and which forms part of a project carried out at the Max-Planck Institute for Psychiatry (MPI) by Dr. Marcus Ising. Funding for this project was acquired by Dr. Marcus Ising in collaboration with Prof. Dr. Gerd Schulte-Körne. A positive ethical decision by the Ludwig-Maximilians-University Medical Division Ethics Committee, Munich, Germany (study ID: 419-15) was granted on 26/08/2015. Recruitment of participants took place between 09/2015 and 03/2017. Data from participants in this study were included in Publication I. When I started working at the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy in 04/2016, the study population and selection of measures had already been fixed. In addition, the positive ethical decisions were granted.

Prof. Dr. Gerd Schulte-Körne and PD Dr. Ellen Greimel supervised the studies. My role in these studies consisted in project administration and recruitment of the participants for the case and control groups. I was also involved in testing the participants, i.e., by conducting the extensive diagnostic interviews with participants and parents and in the subsequent evaluation of the results. I was also involved in collecting questionnaires and handling sali-

va kits as well as in preparing datasets (questionnaires and saliva samples) for the transport to the MPI. These tasks were also conducted by my colleagues Lisa Feldmann and Verena Pehl who investigated different research questions in the context of the two studies, as well as by a study nurse and a research assistant. I was also responsible for the correspondence with the MPI concerning issues such as planning the data transfer, data analyses and interpretation, as well as discussing research questions. Moreover, I was taking care of safeguarding quality control of the two extensive data sets and I preprocessed and merged the two data sets from both studies for data analyses. I conceptualized the research questions, conducted data analyses and interpreted the findings for Publication I under supervision of PD Dr. Ellen Greimel, Prof. Dr. Gerd Schulte-Körne and Dr. Marcus Ising. I also wrote and revised the manuscript of publication I supervised by PD Dr. Ellen Greimel and Prof. Dr. Gerd Schulte-Körne.

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Abbreviations

MD	Major Depression
SNP	Single nucleotide polymorphism
PRS	Polygenic risk score
HPA-axis	Hypothalamic-pituitary-adrenal axis
DNA	Deoxyribonucleic acid
GR	Glucocorticoid receptor
GWAS	Genome-wide association study
G×E	Gene-environment interaction
CNV	Copy number variant
MPI	Max-Planck Institute

Publication I: Interactions between *FKBP5* variation and environmental stressors in adolescent Major Depression

Piechaczek CE, Greimel E, Feldmann L, Pehl V, Allgaier A-K, Frey M, Freisleder FJ, Halldorsdottir T, Binder EB, Ising M, Schulte-Körne G. Interactions between *FKBP5* variation and environmental stressors in adolescent Major Depression. *Psychoneuroendocrinology*. 2019; 106:28-37. doi: 10.1016/j.psyneuen.2019.03.025.

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Publication II: Polygenic risk: predicting depression outcomes in clinical and epidemiological cohorts of youths

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Eidesstattliche Versicherung

Hiermit versichere ich, Charlotte Elisabeth Piechaczek, an Eides statt, dass ich die vorliegende Dissertation „*Genetic and environmental influences on major depression in youth*" selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe. Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, den 08.01.2020

Charlotte Elisabeth Piechaczek

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