Gene × environment interactions in the prediction of response to antidepressant treatment

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Abstract
Major depressive disorder (MDD) is responsible for an increasing individual and global health burden. Extensive research on the genetic disposition to develop MDD and to predict the response to antidepressant treatment has yet failed to identify strong genetic effects. The concept of gene × environment interaction takes into account that environmental factors have been identified as important components in the development of MDD and combines both, genetic predisposition and environmental exposure, to elucidate complex traits such as MDD. Here, we review the current research on gene × environment interactions with regard to the development of MDD as well as response to antidepressant treatment. We hypothesize that gene × environment interactions delineate specific biological subtypes of depression and that individuals with such pathophysiological distinct types of depression will likely respond to different treatments. The elucidation of gene × environment interactions may thus not only help to understand the pathophysiology of MDD but could also provide markers for a personalized antidepressant therapy.

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Introduction
Major depressive disorder (MDD) is an increasing public health problem with high lifetime prevalence in the general population and broad impact on individual and global health. MDD is a polygenetic and multifactorial disease and despite extensive research to find genetic factors for MDD, the so far identified main effects of specific genetic polymorphisms on MDD and/or antidepressant treatment outcome are small and largely lack robust replication across samples (Keers and Aitchison, 2011; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2012). This is despite the fact that twin, family and epidemiological studies estimate that genetic predisposition contributes at least 30–40% of the risk to suffer from MDD. A number of reasons have been brought forward to explain this so-called ‘missing heritability’ and these include the possible heterogeneity of the clinical entity ‘depression’, the contribution of many variants with very small effect sizes or of rare functional variants in addition to common variants as well as the interaction of genetic, environmental and epigenetic factors.

In contrast to specific genetic factors, a number of environmental factors contributing to the development and perpetuation of MDD have been implicated in the pathophysiology of depression for many years (Kessler et al., 1997). Exposure to adverse life events, especially in early childhood have repeatedly been implicated in the pathophysiology of depression (Heim et al., 2008). While exposure to adverse life events increases the risk to suffer from MDD, it does not confer a uniform risk as some individuals seem to be particularly sensitive to such exposures whereas others are not. In addition to moderation by other environmental or developmental factors, this differential susceptibility may be accounted for by genetic moderation of the effects of environmental exposure, within gene × environment interactions.

The concept of gene × environment interaction assumes that genes and the environment interact in a multiplicative way on complex traits. The combined examination of both factors might therefore be more informative for the understanding of the pathophysiology of such disorders, including MDD, than their separate investigation. Susceptibility to MDD and in consequence treatment response is likely the result of a mutual interplay between genetic and environmental factors which are – on their own – neither necessary nor sufficient for the development of the disorder (Sullivan et al., 2000).

Antidepressant drugs, still primarily targeting the monoaminergic neurotransmitter system, as well as
psychotherapy, including cognitive behavioural therapy, are the most commonly used treatments for MDD, either alone or in combination. The response to such treatments exhibits a considerable variation and often several different treatment attempts are needed to achieve remission of symptoms, with a non-negligible fraction of patients developing treatment resistance depression (Trivedi et al., 2006).

Such striking individual variation in treatment response is likely related to biological differences in patients with similar clinical phenotype. Markers that define pathophysiologically similar patients who will respond to similar treatment strategies are therefore of eminent importance in order to optimize antidepressant treatment response by more personalized treatment algorithms (Holsboer, 2008; Klengel and Binder, 2011).

A number of studies have investigated the use of genetic markers to predict antidepressant drug treatment response and recently also response to psychotherapy (Ising et al., 2009; Garriock et al., 2010; Uher et al., 2010; Eley et al., 2011; Keers and Aitchison, 2011). A handful of studies have identified specific environmental factors as predictors of treatment response, especially exposure to child abuse (Nemeroff et al., 2003; Johnstone et al., 2009; Eley et al., 2011; Keers and Aitchison, 2011). A handful of studies have identified specific environmental factors as predictors of treatment response, especially exposure to child abuse (Nemeroff et al., 2003; Johnstone et al., 2009; Eley et al., 2011; Keers and Aitchison, 2011). A handful of studies have identified specific environmental factors as predictors of treatment response, especially exposure to child abuse (Nemeroff et al., 2003; Johnstone et al., 2009; Eley et al., 2011; Keers and Aitchison, 2011).

In this review, we will discuss current results of gene × environment interactions on the development of depression, how such specific interactions may delineate different pathophysiological disturbances and how this could relate to optimized treatment algorithms for MDD.

**Gene × environment interactions in MDD**

The importance of gene × environment interactions on MDD has been predicted by a number of epidemiological studies (Kendler et al., 1995a; Sullivan et al., 2000). In 2003, the first molecular evidence of a polymorphic region in the promoter of the serotonin transporter gene (5-HTTLPR) × stressful life events interaction on the development of depressive symptoms and suicidal ideation was published (Caspi et al., 2003). Subsequent replications, non-replications and meta-analyses of this gene × environment interaction point towards the importance of the type and assessment of the environmental factors in such studies (Munafo et al., 2008; Risch et al., 2009; Karg et al., 2011; Uher et al., 2011). By now, the 5-HTTLPR gene × environment interaction has been implicated not only in MDD but also in other stress related disorders or traits such as post-traumatic stress disorder, suicide attempts, alcohol consumption, eating disorders and others (Gibb et al., 2006; Roy et al., 2007; Laucht et al., 2009; Xie et al., 2009; Kranzler et al., 2012; Stoltenberg et al., 2012). The serotonin transporter has not remained the only gene for which gene × environment interactions have been reported.

We could show for example that polymorphisms in the corticotrophin receptor 1 (CRH1) gene interact with exposure to child abuse to predict adult depressive symptoms in an inner city African–American sample (Bradley et al., 2008) with two CRH1 haplotypes conferring a protective effect on the severity of adult depressive symptoms after exposure to high levels of childhood abuse. This finding has been replicated in some but not all studies. These studies highlight critical factors in gene × environment interaction studies such as the measurement of the environmental factor, the severity of the exposure in the cohort and the definition of the outcome (Polanczyk et al., 2009; Heim et al., 2009; Grabe et al., 2010; Ressler et al., 2010; Kranzler et al., 2011; Laucht et al., 2012). In addition, the interaction of these CRH1 haplotypes and childhood abuse has also been reported for endophenotypes of depression such as the reactivity of the hypothalamic–pituitary–adrenal (HPA) axis (Heim et al., 2009; Tyrka et al., 2009) and neuroimaging phenotypes related to depression (Hsu et al., 2012).

FKBP5, another candidate gene belonging to the stress hormone system has also been shown to account for gene × environment interactions on depression (Appel et al., 2011; Zimmermann et al., 2011) but also on other phenotypes including post-traumatic stress disorder (Binder et al., 2008; Xie et al., 2010), aggression (Bevilacqua et al., 2012) and suicide attempts (Roy et al., 2010). It seems that FKBP5 variants confer a general susceptibility to early-life traumatic experiences that manifest in different psychiatric symptoms possibly by interacting with disturbances in other signalling pathways.

Gene × environment interactions on depressive symptoms have also been reported for the gene encoding the glucocorticoid receptor (GR; Bet et al., 2009), the oxytocin receptor (Thompson et al., 2011), the dopamine D2 receptor (Vaske et al., 2009) and brain-derived neurotrophic factor (BDNF; Kim et al., 2007; Aguilera et al., 2009; Gatt et al., 2009). In addition to the single candidate gene/polymorphism × environment interaction studies mentioned above, gene × gene × environment interactions have also been reported (Kaufman et al., 2006; Wichers et al., 2008; Ressler et al., 2010; Grabe et al., 2012); however, such studies will need very large samples for sufficient power. The same will be true for investigating gene × environment interactions on a genome-wide level (Aschard et al., 2012).

A recent mega-analysis on the genetics of MDD has confirmed on a genome-wide level that main genetic effects in depression are small in size and difficult to replicate across studies (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2012). Gene × environment interactions may be stronger predictors given the impact of environmental factors, especially in early life, on this disorder (Uher, 2009). Genome-wide gene × environment interaction analyses may shed new light on the genetics of MDD. Such
analyses may, however, be complicated by the complexity of such interactions as the same allele that confers risk in interaction with negative environmental factors may be beneficial in a positive environment (Belsky et al., 2009). Integrating combined environmental exposure across development in such analyses will be a daunting task.

To make the most use of gene × environment interactions in understanding pathophysiology and guiding treatment, one must understand their molecular mechanisms. Considering the studies mentioned earlier it becomes clear that different environments interacting with different genes can lead to the same psychiatric symptoms but also that the same gene interacting with the same environmental exposure can lead to diverse psychiatric manifestation in adulthood (see Fig. 1). It will thus be necessary to gain an understanding of the molecular basis of these gene × environment interactions to identify biologically distinct subtypes of depression. By relating specific interactions to distinct pathophysiological disturbances, one could envisage their use in choosing individualized treatments and in identifying new targets for antidepressive therapy. In the following sections, we will briefly review the literature for genetic and environmental predictors of antidepressive therapy as well as the few studies that have investigated gene × environment interactions for this phenotype. Our main focus, however, will be to illustrate how specific gene × environment interactions can lead to specific biological disturbances in MDD that would also profit from different antidepressive treatment strategies.

**Genetics of treatment response in MDD**

Even though the genetic basis of the variability of response to antidepressant treatment is much less established than for the development of MDD itself (Kendler et al., 1995b; Sullivan et al., 2000), a large number of studies have investigated the effects of genetic variants on this phenotype. Most studies, including genome-wide association studies have focused on response to antidepressant drug treatment, both in mono- and combination therapy. While some genetic variants have been replicated in a number of studies, the effect sizes remain very variable or small, making them unsuitable for clinical prediction (Keers and Aitchison, 2011). Even genetic predictors of the pharmacokinetics of antidepressant drugs are not routinely used in the clinic (de Leon, 2009). The lack of strong main genetic effects for this phenotype is supported by a number of genome-wide association
studies, including a meta-analysis across three large studies, that all report no consistent associations (Ising et al., 2009; Garriock et al., 2010; Uher et al., 2010). This suggests a more complex relationship of genetic variation and antidepressant treatment response in which additive or interactive effects of more than one genetic variation influence treatment outcome may be possible (Ising et al., 2009; Horstmann et al., 2010) but could also indicate the importance of including environmental exposure in such analyses.

A handful of studies have reported genetic influences on the outcome of cognitive behavioural therapy (Lonsdorf et al., 2010; Eley et al., 2011; Lester et al., 2012) and electro-convulsive therapy (Anttila et al., 2008). However, genetic predictors of therapeutic options other than antidepressant drugs are not well studied and should be an area of future investigations.

In summary, main genetic effect on antidepressant response seems minor and at least for pharmacodynamic genes, the lack of main genetic effect on the development of depression described in the previous paragraph may have helped to anticipate such negative findings.

Environmental predictors of treatment response in MDD

In addition to other clinical factors, environmental exposure, especially to traumatic experience in childhood may serve as predictor of antidepressant response (Nanni et al., 2012). In fact, childhood abuse has been shown to not only increase the risk and persistence of depression in adulthood (Chapman et al., 2004) but also to influence antidepressant treatment outcome. It has been reported that individuals with a history of early trauma preferentially respond to psychotherapy as compared to a specific antidepressant drug treatment (Nemeroff et al., 2003). A recent meta-analysis across 10 different treatment trials also revealed that treatment response overall is lower in individuals with childhood abuse in contrast to individuals without such an experience independent from the treatment algorithm (Nanni et al., 2012).

Gene × environment interactions in the prediction of antidepressant treatment response

In extension to the earlier-cited studies investigating main genetic and environmental effects, a handful of studies have now been published reporting on how specific polymorphisms and specific environmental exposures interact to predict outcome to antidepressant treatment. The first evidence for gene × environment interactions predicting antidepressant response was reported in 2009. Mandelli et al. showed that experienced life stress according to the Life-events and Difficulty Schedule in the year preceding the onset of a first mood disorder episode interacts with the 5-HTTLPR to predict response to the selective serotonin reuptake inhibitor (SSRI) fluvoxamine (n = 159; Mandelli et al., 2009). Short (s)-allele carriers exposed to a stressor exhibited a poorer treatment outcome in contrast to long (l)-allele carriers, but this was not true for non-exposed s-allele carriers. In fact, previous studies have reported a worse response to SSRI treatment (Serretti et al., 2007) as well as an increased responsiveness to negative life events (Caspi et al., 2010) for s-allele carriers. A similar interaction was observed by Keers et al. (2011). The authors examined the effects of stressful life events and the 5-HTTLPR in the GENDEP cohort, a prospective part-randomized pharmacogenomics trial with >800 participants treated with either escitalopram (an SSRI) or nortriptyline (a tricyclic antidepressant; Keers et al., 2011). Life events were assessed using the List of Threatening Experiences Questionnaire in a period of 6 months before treatment. Here again, s-allele carrier status of the 5-HTTLPR was a negative predictor of response to escitalopram in the exposed but not the non-exposed group (n = 383). This interaction was specific to SSRI treatment and not seen in patients treated with nortriptyline (n = 291). No interaction between the 5-HTTLPR and stressful life events was seen in a cohort of 290 depressed patients, treated at doctor’s choice (Bukh et al., 2010). These authors also did not observe any interaction of life events and polymorphisms in the genes BDNF, COMT, TPH1, ACE, HTR1A, HTR2A, HTR2C on treatment response in a naturalistic setting (Bukh et al., 2010). In these studies, the definition of stressful life events included stressors in a period 6 months before onset of the current depressive episode using the Interview for Recent Life Events.

Two other gene × stressful life event interactions on treatment response from the GENDEP sample have been mentioned in a review article by Keers (2012). Exposure to stress was predictive for treatment outcome in carriers of the T-allele of rs1360780 in FKBP5 and the G-allele of rs110402 in CRHRI, both alleles that have been proposed to confer stress sensitivity (Keers, 2012).

Only two studies have so far investigated the early trauma × genotype interaction on antidepressant treatment response. Xu et al. (2011) investigated gene × environment interaction in depressed in-patients (n = 308) assessing early life trauma using the Childhood Trauma Questionnaire and the Life Events Scale for stressful life events in the year preceding the treatment (Xu et al., 2011). Patients were treated for 6 wk and the authors noted a significant interaction of a single-nucleotide polymorphism (SNP) in the norepinephrine transporter SLC6A2 with childhood abuse to predict worse treatment outcome. This group also reported a significant HTR1B SNP × recent stress interaction as well as a TPH2 SNP × childhood abuse interaction on reduced antidepressant response in the same sample (Xu et al., 2012; see Table 1).

Although these findings are not replicated, they suggest a possible explanation of inconsistent findings of treatment response in MDD when main effects of genetics
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SSRI, Selective serotonin reuptake inhibitor; s-allele, l-allele, short and long allele respectively; TCA, tricyclic antidepressant.
or environmental exposure alone are considered. While these first findings may be encouraging, they also highlight the difficulties of gene × environment interaction research. A broad variety of possible environmental factors have been reported to impact MDD and antidepressant treatment response and there are numerous ways to assess them. Environmental exposure can have protective and detrimental effects and can act on an individual and group level, with a high number of possible combinations and interactions. The earlier mentioned studies alone have used five different measurements of environmental stressors that potentially measure different types of stress exposure and stress perception that makes comparisons across studies difficult. Additionally, these studies measured environmental factors of varying intensities at different time-points. For example, Mandelli et al. interrogated life stress in the year preceding the first episode of the mood disorder, i.e. at a variable time-point before the current episode. Bukh et al. assessed life stress within 6 months before the onset of the current episode and Keers et al. evaluated life stress within 6 months before treatment. Timing of a stress exposure is likely critical for these interactions and renders the direct comparison of the above studies difficult to impossible.

In addition to proximal stressors occurring before the onset of a disease or treatment, earlier stressors such as childhood abuse may interact with more recent stressors to predict unfavourable outcome of standard treatment. Even without considering such environment × environment interactions, early life stress is largely unexplored with regard to gene × environment interactions on treatment response as mentioned earlier. In addition, the assessment of early trauma has been shown to have a strong impact on gene × environment interaction in MDD, where most consistent results came from structured interviews and objective governmental databases, whereas self-reported stressors were less comparable (Karg et al., 2011).

No gene × environment interaction study has so far investigated response to non-pharmacological treatment or prediction of differential response to different treatment modalities but first genetic studies point towards the possibility that genetic predictors for response to psychotherapy may be different from the ones for antidepressant drug treatment. As suggested by Eley et al., the s-allele of 5-HTTLPR, which conveys risk for depression in response to stress, seems to positively moderate the effect of cognitive behavioural therapy but is a negative predictor of response to drug treatment, especially SSRIs (Serretti et al., 2007; Eley et al., 2011).

Given the paucity and diversity of the published gene × environment studies in the prediction of antidepressant response, the field would certainly profit from large studies that explore similar or the same environmental measure. It is, however, difficult to recommend what should be considered state of the art for such studies. While it is clear that prospective assessment of the environment is superior to retrospective assessment and assessment by structured interviews or third-party datasets to self-reported exposures, it is less clear which stressors would have the most impact, i.e. would an exposure to a stressor before the onset of the first depressive episode be of more relevance to such gene × environment studies than stressful life events in the weeks before treatment of the current episode. In addition, one needs to keep in mind that even if adverse life events would be recorded in a standardized and optimal fashion, the impact of these life events is likely to be moderated by positive environmental factors such as the presence of a supportive surrounding. Standardized instruments to measure positive environmental factors are much less established. Large exploratory studies, recording a broad spectrum of environmental variable might be helpful in identifying the most relevant environmental variables for such studies. In addition, the development of biomarkers for environmental exposure, such as DNA methylation in peripheral blood cells as described in Borghol et al. (2012) might be helpful in standardizing such analyses.

**Potential molecular mechanism of gene × environment interactions; implications for MDD treatment**

While the number of reported gene × environment interactions is increasing, the molecular mechanisms behind such interactions have so far not been elucidated. Studies using intermediate phenotypes of stress reactivity such as neuroendocrine and neuroimaging measures may help to dissect mechanisms at least on the systemic level and we illustrate this using the interaction of stressful life events with the 5-HTTLPR on the development and treatment of MDD. The 5-HTTLPR has been shown to impact the neural processing of stressful or emotional stimuli in a number of neuroimaging studies investigating amygdala reactivity as well as the connectivity between amygdala and cingulate cortex (Pezawas et al., 2005; Munafò et al., 2008). The s-allele that results in a decreased function of the serotonin transporter, and thus possibly changed serotonergic signalling, seems to lead to altered brain activation by emotional stimuli. For example, children carrying the s-allele of the 5-HTTLPR exhibit stronger brain activation in regions known to be involved in emotional processing and MDD during a transient state of sadness than children with the l-allele (Fortier et al., 2010). In a study by Alexander et al. (2012), the presentation of fearful faces resulted in an enhanced activation of the amygdala in healthy s-allele carriers with a history of stressful life events and an enhanced connectivity between amygdala and hypothalamus, a brain region associated with stress hormone activation (Alexander et al., 2012). In extension of the earlier mentioned findings, the exposure to stressful life events in healthy individuals carrying the s-allele has been associated with an increased cortisol release in response to psychological.
stressors (Alexander et al., 2009). Thus, a genetic predisposition in the regulation of serotonergic neurotransmission could lead to differences in emotional processing in interaction with stress exposure, thereby increasing vulnerability to psychiatric disorders. The 5-HTTLPR × environment interaction on the development of depression may be influenced in particular during periods of heightened plasticity of brain regions that depend on serotonergic transmission in childhood. The s-allele that confers risk in the presence of a stressor may, however, also have beneficial effects when exposed to a positive environment (Belsky et al., 2009; Pluess et al., 2010; Hankin et al., 2011) and such alleles should therefore be better termed environmental reactive alleles. This increased sensitivity to emotional stimuli may also explain the observed better treatment outcome of s-allele carriers to psychotherapy (Eley et al., 2011).

While these studies have reported effects of gene × environment interactions on a system-wide level, the molecular mechanisms underlying these interactions remains unclear.

Epigenetic changes by DNA methylation or histone modifications are prime candidates for molecular mechanisms of gene × environment interactions because they are mutually responsive to genetic variations and environmental exposure, thus integrating both influences on a molecular level. In fact, the genetic predisposition is stable and therefore not directly accessible to effects of the environment. Instead, epigenetic modifications allow a long-term and stable modification of the DNA to alter gene expression (Szyf, 2009) that could be conferred in a genotype-dependent manner. DNA methylation refers to the modification of the cytosine residue, predominantly in CpG dinucleotides, by a methyl group, but other modifications have also been described (Bhutani et al., 2011). Classically, DNA methylation in promoter regions has been shown to repress the transcription of the gene by differential binding of transcription factors and histone modifying enzymes, mainly involved in tissue differentiation (Jaenisch and Bird, 2003). More recent studies have, however, indicated that DNA methylation outside of classical promoter regions or CpG islands are of equal or even higher importance for the fine tuning of gene expression (Suzuki and Bird, 2008), a function likely more relevant to psychiatric disease.

As mentioned earlier, environmental experience can have long-lasting effects on gene expression by inducing epigenetic changes such as DNA methylation and this has been shown in a number of animal models of early life stress (Weaver et al., 2004; Tsankova et al., 2006; Murgatroyd et al., 2009; Elliott et al., 2010). In human post-mortem samples, McGowan et al. were able to show that childhood abuse leads to hypermethylation in a promoter region of the glucocorticoid receptor gene (NR3C1). This hypermethylation was associated with a reduced binding of the NGF1α transcription factor and subsequently a reduced expression of NR3C1 mRNA (McGowan et al., 2009). These data fit well with the often observed dysfunction of the glucocorticoid receptor–stress hormone axis in depression, especially when occurring as consequence of early life trauma. By now, there are a growing number of studies investigating the effect of early experience on DNA methylation (Szyf, 2009) mostly on a candidate gene level. But there are also genome-wide studies linking the environment in early life to DNA methylation. For example it has been shown that children raised in institutionalized care exhibited a different methylation profile in peripheral blood compared to children raised by their biological parents (Naumova et al., 2012). Furthermore, socio-economic status in childhood seems to influence the genomic methylation pattern in peripheral blood DNA in adulthood possibly linking childhood socio-economic status to adult morbidity and mortality (Borghol et al., 2012). A recent study in human post-mortem tissue by Labonte et al. compared differentially methylated regions of individuals with and without exposure to childhood abuse in the hippocampus. This so far largest study in human brain tissue found broad effects of child abuse on the epigenome affecting different functional pathways by orchestrated hyper- and hypomethylation of selected promoter regions (Labonte et al., 2012). This indicates that early environment influences DNA methylation across the genome, to orchestrate long-term changes on a systemic level.

While an increasing number of studies document long-term epigenetic effects of early environment, little is known about how this is moderated by genetic variation. A number of studies have shown that DNA methylation can be sequence-specific, i.e. specific to genetic variation (Schalkwyk et al., 2010; Lienert et al., 2011) and here a number of different mechanisms are conceivable. Genetic variations may be associated with a differential accessibility of chromatin to DNA modifying enzymes (Kadota et al., 2007; Kerkel et al., 2008). It could also directly modify sites that are under epigenetic control (Mill et al., 2008), such as disruption or creation of cytosine–guanine dinucleotides. Genetic variations in genes that are upstream of genes effecting epigenetic changes could also indirectly modify the downstream events.

Our group recently demonstrated an epigenetic mechanism for a gene × environment interaction of polymorphisms in the GR-co-chaperone gene FKBP5 with childhood abuse on the risk of developing post-traumatic stress disorder in adulthood (Klengel et al., 2012). FKBP5 binds to the GR complex via heat shock protein 90 and thus reduces the affinity for cortisol resulting in a less active GR. In fact, only in FKBP5 risk allele carriers, child abuse is associated with a DNA demethylation of glucocorticoid response elements within the FKBP5 locus. This lasting demethylation leads to enhanced FKBP5 transcription and in consequence GR resistance and dysregulation of the HPA axis. This gene × environment interaction that has been associated with a number of
different stress-related psychiatric disorders and symptoms may be explained by a common, epigenetically driven molecular mechanism. The underlying de-repression of FKBP5 might be targeted by FKBP5 receptor antagonists (Schmidt et al., 2012) and could be helpful in treating a number of different syndromes that stem from the same FKBP5 x child abuse interaction that results in different symptom presentations likely due to interaction with other environmental, developmental and genetic moderators.

Figure 1 illustrates how combinations of environmental and genetic factors could result in different molecular disturbances that lead to a similar clinical presentation. An individualized antidepressant strategy would therefore need to be based on the underlying molecular mechanism and cannot rely on symptom presentation.

Conclusions and outlook

The analysis of main genetic effects to identify markers for a personalized treatment of MDD has not been very successful so far. This is likely due to the fact that depression per se is a heterogeneous condition influenced by both genetic and environmental factors. A number of gene x environment interaction studies now implicate the interaction of both genetics and environmental factors on the development of MDD and response to antidepressant treatment. While the latter offer a first support for their use to predict response to current antidepressant treatments, the real strength of such studies will lie in identifying distinct molecular mechanisms underlying the development of MDD that could then be specifically targeted in patients to allow personalized medicine relying on pathomechanisms. It is also likely that the identification of such environmentally reactive alleles could identify patients who would profit more from positive interventions by psychotherapy than others.

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