Gene, brains, and environment—genetic neuroimaging of depression
Georg Northoff

Depression, conceptualized as major depressive disorder (MDD), is a complex psychiatric disorder with multiple behavioral changes and alterations in various brain regions. Biochemically, serotonin and other substances like GABA, glutamate, norepinephrin, adrenaline/noradrenaline play an essential role in the pathogenesis of MDD. The paper reviews recent human neuroimaging findings on how the genes underlying these biochemical substances modulate neural activity, behavior, and ultimately clinical symptoms. Current data provide solid evidence that genes related to serotonin impact emotion-related neural activity in the amygdala and the anterior cingulate cortex. By contrast, evidence is not as strong for genes related to biochemical substances other than serotonin and other regions of the brain. The review concludes with discussing future genetic, neural, and clinical challenges that point out the central role of gene × environment and brain × environment interactions as genetic and neural predispositions of depression.

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Introduction
Depression is a psychiatric disorder that is characterized by various symptoms including motor, vegetative, cognitive, and affective abnormalities as they are subsumed under the concept of major depressive disorder (MDD) [1**]. Neurobiologically, MDD shows altered neural activity in various regions of the brain that are involved in emotion processing including the amygdala, the prepontual anterior cingulate cortex (PACC), the dorsolateral prefrontal cortex (DLPFC), and subcortical regions like the midbrain [2,3].

Biochemically, various substances like serotonin, GABA, glutamate, norepinephrin, and many others are assumed to play a major role in MDD [2]. Among them serotonin is probably one of the most significant ones since (i) changes in serotoninergic function (i.e. receptors, metabolism, reactivity) have been observed in MDD, and (ii) therapeutic efficacy of serotoninergic drugs in MDD is well documented [4].

Investigations in healthy subjects described relationship between serotonin-related genes and psychological and neural changes mirroring the ones in MDD [5,6*]. This let to extensive research of especially serotonin-related genes in genetic neuroimaging of both healthy and MDD subjects. That has recently been complemented by investigating genes controlling other biochemical substances like BDNF, neuropeptide Y, CREB, and so on [7,8]. The first part of this paper therefore reviews the neuroimaging findings on serotonin-related genes and the ones on genes implicated in biochemicals other than serotonin. This is a complemented by a second part that discusses the genetic, neural, and clinical challenges for future neuroimaging of depression.

(I) Review of recent findings
Serotonin-related genes and neural activity
The insertion/deletion of the promoter polymorphism (5-HTTLPR) of the serotonin transporter gene (SLC6A4) has been shown early on to modulate anxiety-related personality traits [9], which though was only partially replicated in subsequent studies [6*,10*]. Subsequent studies demonstrated that S-allele (s = short) carriers of the 5-HTTLPR-promotor polymorphism show increased neural activity in the amygdala in response to negative emotional stimuli when compared to L-allele carriers [5]. (See [6*] for an overview.) Subsequent studies demonstrated that the S-allele impacts also the volume and the resting state activity of the amygdala [11,12] as well as its functional connectivity to the PACC [10*,13,14] Error! Bookmark not defined (Table 1).

In addition to the 5-HTTLPR polymorphism, other genes implicated in serotoninergic metabolism have been shown to modulate emotion-related neural activity in the amygdala and amygdala-cingulate functional connectivity (and 5HT-1a receptor density). One of them is the HTR1a gene that controls the expression of the 5-HT1a receptor density with the C-allele carriers showing larger effects than the ones with the G-allele.

Another gene impacting emotion-related activity in the amygdala is the MonoAminoOxidase-A (MAOA) that as
enzyme is involved in the degradation of 5-HT and norepinephrine; the L alleles and H alleles impact the amygdala activity, volume, and connectivity in differential (yet unclear because of sometimes contradictory effects of L-allele and H-allele effects) ways [6*,15,16].

Finally, there is the tryptophan hydroxylase 2 Gen that codes the tryptophan hydroxylase and its T-alleles and G-alleles that provide an enzyme for the synthesis of serotonin [4]. Besides impacting emotion-related neural activity in the amygdala and amygdala-cingulate functional connectivity, these genes also modulate, partly, hippocampal volume [17].

While these findings were mainly observed in healthy subjects, they were also observed in patients with MDD [4,6*]. This is even more relevant since the amygdala and the PACC are indeed core regions in the pathophysiology of MDD: Both the amygdala and the PACC show abnormally increased resting state activity [1**,2,18,19] and abnormal stimulus-induced activity to especially negative stimuli in MDD [1**,2,20,21].

Taken together, these findings suggest that the levels of both resting state and stimulus-induced activity in the amygdala and the PACC/ACC are, at least partly, controlled by serotonin-related genes. This raises the following question: What are the psychological mechanisms that mediate the impact of serotonin-related genes on the emotion-related neural activity in these regions? One possible psychological candidate is stress, aversive and stressful life-events as they can be often found in the biography of MDD patients [22].

This has been addressed in recent studies. Drabant et al. [23] threatened subjects with an electric shock and focused on the anticipatory period. They observed increased neural activity in the aversive network (amygdala, hippocampus, anterior insula, anterior cingulate, thalamus, precentral, caudate [24]) in S-carriers when compared to the L-carriers of the 5-HTTLPR polymorphism. They suggest that aversion and stress are essential in mediating the effects of the 5-HTTLPR polymorphisms on neural activity in amygdala and PACC.

The assumption of aversive-related and thus stress-related mechanisms is further supported by another study stemming from the group around Alexander et al. [25**]. S-carriers of the 5-HTTLPR polymorphism with increased stressful life events in their personal history showed elevated amygdala activity during fearful faces when compared to those without stressful life events. Subjects with stressful life events also showed increased cortical reactivity as well as increased functional connectivity of the amygdala with the hypothalamus that controls neuroendocrine regulation of stress-related
hormones like Cortisol. The authors conclude that stressful life events may induce both neural and neuro-endocrine hyper-reactivity (as well as hippocampal volume reduction [26]) in the S-carriers.

These most recent findings refine the role of serotonin-related genes even further in that they suggest their central role in mediating aversive and stressful life events. Besides the merely neural effects, serotonin-related genes thus seem to mediate specific interaction effects between the brain and the environment and thus what is described as gene–environment interaction (see [27] as well as below for more details).

Early aversive and stressful life events often occur in the biography of MDD patients [22]. Serotonin-based gene–environment interaction may thus be central in mediating the above described abnormalities in resting state and stimulus-induced activity in PACC and amygdala in MDD. However, future studies are needed to investigate such gene–environment interaction effects on especially the abnormal resting state in MDD. Besides genetic and neural variables, one may thereby want to include measures of both neuro-endocrine stress-related functions (like cortisol) and biographical stressful aversive life events (like childhood trauma) in future experimental designs.

Besides stressful and traumatic life events, 5-HTTLPR promotor polymorphism may also mediate the modulation of cognitive functions like attention and executive functions including their underlying neural substrates. Beevers et al. [28] observed the volume of the lateral prefrontal cortex (LPFC) to be inversely related to the performance in an emotional attention task in carriers of the S-allele of the 5-HTTLPR promotor polymorphism. This is complemented by Holmes et al. [29]: They demonstrated impaired performance in action monitoring (e.g. Flanker task with conflict and error) and abnormal anterior cingulate activity in S-carriers of the 5-HTTLPR polymorphism a pattern similar to the one observed in MDD patients.

This is particularly interesting for MDD: These patients show decreased resting state activity in the LPFC and especially the DLPFC [2,30] as well as cognitive deficits in emotional attention and action monitoring [4,20]. The initial neuroimaging findings described above suggest that these neural and cognitive changes may, partly, be under serotonergic genetic control that may be abnormal in yet unknown ways in MDD. Since both PACC resting state hyperactivity and DLPFC resting state hypoactivity seems to be controlled by serotonin-related genes, one may assume a specific network-based rather than region-specific effect (see below for further discussion).

**Other non-serotonin-related genes and neural activity**

Besides genes coding for serotonin, genes for other biochemical implicated in the pathophysiology of MDD are currently investigated. One of them is the gene for Brain derived neurotrophic factor (BDNF) with especially its Single Nucleotide Polymorphism (SNP) Val66Met polymorphism that modulates the activity-dependent secretion of BDNF (and more generally neuroplasticity).

While the findings of the Val66Met polymorphism with regard to amygdala activity are rather inconsistent at this point [6*], it is more robustly associated with hippocampal volume reduction: The carriers of the Met allele show stronger volume reduction in the hippocampus when compared to those carrying the Val allele in both healthy and MDD subjects [4,6*,7,31].

Apart from the BDNF gene, recent studies focused on the genes related to neuropeptide Y whose expression seems to be reduced in MDD: Domschke et al. [32] observed increased amygdala activity during facial emotions in the carriers of the rs16147 C allele of the NPY gene. While Mickey et al. [8] demonstrated differential neural activities in PACC in response to negative stimuli between low-NPY and high-NPY expression groups.

Another protein involved in the pathophysiology of MDD is CREB. CREB stands for cyclic adenosine monophosphate response element-binding protein 1 (CREB1) that is part of the neuroplastic pathway and central for the brain in adapting to stress. Different alleles of the gene coding for CREB1 were associated with differential activity in emotion-related regions like the amygdala and the anterior cingulate. Interestingly, these effects were further amplified by a history of childhood adversity [33,34**].

Finally, genes coding for proteins that are implicated in reward processing like the COMT [35], TREK (expressed in basal ganglia) [36], or the D3-receptor [37] are also associated with specific neural activity changes in reward-related regions like the nucleus accumbens/ventral striatum and the ventral prefrontal cortex.

Taken together, recent investigations target genes coding for biochemical substances other than serotonin implicated in the pathophysiology of MDD. Since these target the genetic controls of substances that have been shown to be relevant in both animal models of MDD and human MDD, they nicely bridge the gap between animals and humans [2].

Most of these genes targeted in these studies control biochemicals strongly implicated in stress like BDNF or CREB. These findings thus further emphasize the genetic control of the neural effects of stressful and aversive life events, for example, gene–environment interaction and brain–environment interaction as I will call further down. What remains open though is whether these findings mainly obtained in healthy subjects also
apply to MDD patients and their specific kind of early traumatic aversive life events like material or paternal neglect [22].

**II. Challenges and outlook**

Neurogenetic functional imaging studies in depression (and other psychiatric disorders) encounter empirical-experimental and conceptual-methodological challenges on different levels, genetic, neuronal, and clinical. These shall be discussed briefly in the following.

**Genetic challenges**

*Beyond polymorphisms*

The focus in most studies is on comparing neural and behavioral effects of different SNPs of a particular gene, the candidate gene. However, the genome is much more complex. It shows various copies of the same materials, so-called ‘copy number variants’ (CNV), that carry deletions, insertions, duplications, and probably yet unknown changes related to the copying processes. These may be highly relevant in especially psychiatric disorders [38*] where the number and/or quality of mistakes during the copying process may exceed a certain yet unknown threshold.

The exact mechanisms how such CNV are generated remain unclear at this point. One possible way how mistakes in the copying of the genome are generated may be via interaction with the environment, that is, gene × environment interaction. One may for instance assume strong traumatic and aversive life events may interfere with the copying process. Thereby, especially aversive life events may create a tendency and thus predispose to false-positive or false-negative copying of genes. If so, one would expect increased degrees of early traumatic and stressful life events to go along with an increased number of CNV. Whether that can account for abnormal CNV and the increased presence of certain polymorphism in MDD (and other psychiatric disorders) remains unclear though.

*Beyond single genes*

Most studies in the context of MDD focused on single genes, candidates genes, and tested their neuronal effects in an a priori manner. Since this restricts the empirical results and does not allow for an exploratory more a posteriori approach, great hope is placed in genome wide association studies (GWA) and larger samples [4,6* ,38*].

The current results are based mostly on candidate genes with an a priori approach yielded only partly consistent results. A more exploratory a posteriori genome wide approach may thus be useful and complementary. One may then for instance test for specific gene–gene interaction (like between two polymorphisms that is described as ‘epistasis’; see for instance Pauli et al. [39] who investigated the interaction between dopamine-related and glutamate-related polymorphisms on neural activity during a verbal fluency task) as based on the exploratory a posteriori results. Whether this though will yield more conclusive results remains open at this point.

Finally, one may also want to consider processes associated with the expression of genes like the CpG methylation level or the mRNA level. The methylation status of genes like the one of the glucocorticoid receptor or the serotonin transporter may be central in assessing epigenetic factors [40–42]. That may be central in understanding how gene × environment interaction predisposes (see below for explanation of this term) subsequent depression via modulating neural activity. Future studies may therefore want to combine the methylation processes of specific genes with corresponding neural measures in fMRI, EEG, or PET.

*Beyond genes*

The results point out the central role of gene–environment interaction [27,43]. While the environment is defined and operationalized by different social functions, their genetic control is just recently being explored. Genes controlling the neural and endocrine expression of social and especially stressful life-events need to be investigated. Hsu et al. [44*], for instance, investigated genes controlling the corticotropin-releasing hormone receptor 1 (CRHR1) that controls the neuronal and neuro-endocrine responses to life events and stress. They observed the G-allele and A-allele carriers of the CRH receptor 1 (CRHR1) gene to differ in their neural response to emotional stimuli in several regions. These included the amygdala, PACC, hypothalamus, nucleus accumbens with differences in these regions also occurring between healthy and MDD subjects.

Another example in this direction is the investigation of genes controlling substances like oxytocin, vasopressin, and MAO that modulate social behavior like bonding or aggression [45,46*]. Taken together, these findings provide further evidence for the central role of gene–environment effects on neural activity (see below).

They may also help in specifying the meaning of the concept of ‘environment’ that includes several distinct types (phenomenal-experiential and physical) and tokens of life-events [27]. This is of special relevance given that MDD is often triggered by specific life-events like the experience of neglect by superiors or partners [22,47].

**Neural challenges**

*Beyond serotonin*

The initial studies focused on serotonin-related genes. In the last 2–3 years, candidates genes for substances other than serotonin are considered. As described above these focused on genes controlling proteins like BDNF and CREB that mediate stressful life events. By contrast,
genes for biochemical substances like GABA and Glutamate as central transmitters that constitute the excitation-inhibition balance (EIB) in especially the cortex remain to be investigated though. The EIB seems to be abnormal in MDD as it is manifest in especially abnormal resting state activity in both PACC (increased) and DLPFC (decreased) [1,2]. The exact neuronal and especially neurogenetic mechanisms of such abnormal medial-lateral resting state activity pattern in MDD remain unclear though.

Neurogenetic investigation of the genes underlying GABA (e.g. GAD1 gene may serve for instance as candidate gene) and Glutamate (e.g. genes for the various receptors (NMDA, AMPA, etc.) and the reuptake transporters) (and of other amino acids; for instance [48–50] may shed light on the genetic underpinnings of the EIB (see also [51]). The GABA-based and Glutamate-based EIB of the resting state may thereby be treated as final common neurophysiological pathway or convergence point between stressful life events and genetic control of GABA and Glutamate.

Given that MDD is a resting state disorder and shows strong changes in both GABA and Glutamate [1**,2,52], the neuro-genetic control of the EIB in both the resting state and stimulus-induced activity may be central to explore in the future in both healthy and MDD subjects. Besides Glutamate and GABA other substances like Dopamine and their respective genes may also modulate the resting state activity as for instance its functional connectivity between subcortical and cortical regions [53*]. Future studies in MDD may therefore want to for instance combine biochemical measures (as with PET and MRS) of GABA and Glutamate with intracranial recording (for the EIB), functional fMRI, and genetic (polymorphisms) measures.

**Beyond regions**

The main focus has been so far on regions of the limbic network like the amygdala, the hippocampus, and the PACC. By contrast, genetic modulation of other regions like the dorsolateral prefrontal cortex (DLPFC) or subcortical regions like the thalamus, the PAG, the tectum, or the ventral striatum remains largely unexplored. This though is of central importance since these regions do also show abnormal activity during both resting state [1,2] and stimulus-induced activity in MDD [3]. Rather than impacting one particular region, genes may modulate the relationship between regions.

This is for instance documented in the above described effects of the 5-HTTLPR promotor polymorphism on amygdala-cingulate functional connectivity (see above). Another trans-regional relationship worth investigating may be the one between medial and lateral prefrontal cortex: Both regions show opposite neural activity changes during cognitive and emotional stimulation with such reciprocal modulation being abnormally reduced in MDD [54,55].

One may also want to move beyond mere functional connectivity to more complex measures of global brain function like the small world organization, graph theory, variability, frequency fluctuations, information integration, entropy and structural connectivity [56]. Thereby, more complex ways like independent component analysis (ICA) and structural equation modelling (SEM) of integrating both genetic and environmental life-event data into the analysis of structural and functional MRI datasets may be helpful in tightening the link between genes and neural activity [27,57].

Finally, neurogenetic imaging studies focused so far mainly on fMRI and spatial patterns of activity implying what can be described as ‘spatial neurogenetics’. By contrast, temporal patterns, that is, ‘temporal neurogenetics’, and especially different frequencies of neural activity fluctuations like theta, delta, alpha, and so on, frequencies have rather sparsely been linked to genetic control.

For instance, Lee et al. [58] described that the 5-HTTLPR gene seems to modulate gamma frequency power (30–50 Hz) in the resting state of healthy subjects (see also Başar and Güntekin [59], p. 261–4 for further discussion of genetic control of EEG-meaures). Future studies may want to combine both fMRI and EEG. This may allow to investigate whether certain spatiotemporal patterns of neural activity like between PACC and DLPFC during both the resting state and stimulus-induced activity are controlled and predisposed (see below for more detailed explanation of the term ‘predisposed’) by particular genes (or their polymorphism or copied number variants).

**Beyond the brain**

The brain shows fluctuations in its intrinsic activity that are strongest in low frequency ranges like 0.001–0.1 Hz (e.g. infraslow) and 1–4 Hz (e.g. delta) [47]. Once stimulus-induced activity sets in, these lower frequencies are complemented by higher frequency ranges (alpha: 8–12 Hz, beta: 12–20 Hz, and gamma: 20–40 Hz). While the higher frequency ranges like alpha, beta, and gamma have been well investigated and detailed with regard to affective, sensorimotor, and cognitive functions [63], the exact purpose of lower frequency ranges (delta and infraslow) remains unclear.

One possible function of these slow frequency fluctuations may be their coupling to the occurrence of stimuli across time: The low frequency fluctuations (infraslow and delta) can shift the onsets of their positive and negative parts to align them to the onset of the stimuli
in the environment (especially when the latter are presented in a rhythmic way) [60–63]. Such ‘phase shift’ or ‘phase alignment’ may be central in linking the brain’s intrinsic activity with its low frequency fluctuations to the presentation of stimuli in the environment across time.

Phase shifting of the resting state’s low frequency fluctuations may provide a mechanism by means of which the brain can interact directly with the environment. Analogously to gene × environment interaction, one may therefore want to speak of brain × environment interaction, that is, B × E interaction. It may now be interesting to see how B × E interaction is controlled by the genes and the latter’s interaction with the environment, that is, G × E interaction. Hence, the above described phase shifting of the resting state’s low frequency fluctuations may be a point of convergence between G × E and B × E interaction.

This may be of special importance in MDD where the patients and their brain’s resting state’s low frequency fluctuations seem to be decoupled from their respective environmental surroundings [1**]. Future studies in both healthy and MDD subjects want to directly link G × E interaction with B × E interaction with regard to for instance phase shifting (which as one subset may also include what Hyde et al. [27] describe as IG × E, the imaging of the gene × environment interaction). Finally, given the strong evidence of experience-dependence and context-dependence of both neural and genetic activity, one may assume both G × E and B × E interaction to be central and thus of ‘biological (or more correctly ‘bi-social’) primacy’ [47].

### Clinical challenges

#### Beyond intermediate phenotypes

The early genetic studies demonstrated that there is no direct link from genes, that is, the genotype, to clinical symptoms, that is, the clinical phenotype. This let to the introduction of the concept of ‘intermediate phenotypes’ [63]: Intermediate phenotypes describe neurobiological or neuropsychological traits that are linked to both genetic heritability and clinical disorder (see also the related concept of ‘endophenotype’ [54]. The above described findings of for instance differential amygdala activity and amygdala-cingulate functional connectivity in S-carriers and L-carriers can be regarded such intermediate phenotype that mediates between the 5-HTTLPR gene and the abnormal affective symptoms in depression.

Despite the success of finding intermediate phenotypes for different genes, the question for their specificity has to be raised on various levels. There is the question for the genetic specificity: Besides the 5-HTTLPR gene other genes both serotoninergic and non-serotoninergic, there are clearly other genes involved in controlling emotion-related activity in the amygdala as for instance described above. And there is also the problem of psychological specificity: Does the candidate gene and its polymorphisms really modulate specifically emotion-related processing in the amygdala rather than other function like vegetative functions or aversion that are also processed in the same region?

Finally, there is the issue of clinical specificity: The same neurogenetic changes associated with especially serotonin-related genes and the amygdala cannot only be observed in MDD but also in psychiatric disorders like panic disorder and social anxiety disorder [15]. Future studies are thus necessary to specify the concept of the ‘intermediate phenotype’ in genetic, psychological, and clinical regard.

#### Beyond clinical phenotypes

One of the main problems in especially the neurogenetics of psychiatric disorders is the clinical assumption of nosological entities that function as clinical phenotypes like MDD or schizophrenia. Nosological entities are based on the categorization of behavior by the observer, for example, the clinician, and are thus subjective. Instead, one would prefer, as in other disciplines of medicine, objective and brain-based (rather than observer-based) criteria for classifying behavior and clinical symptoms.

One way to deal with the problem of nosological entities is to resolve them into different subentities or ‘subphenotypes’ [64]. In the case of MDD this would result in increased stress-responsivity, increased self-focus, and anhedonia as ‘clinical subphenotypes’ [1,54]. Or one may go even further and dissolve the nosological entities completely (‘denosologization’; Scharinger et al. [6*]) and assume only syndromes that can occur across the different entities. For instance, catatonia is a psychomotor syndrome (showing stupor, mutism, posturing, catalepsy, and behavioral and affective abnormalities) that occurs in both MDD and schizophrenia as well as in other psychiatric and neurological (and even medical) disorders [65].

To shed some light on the ‘correct’ classification, future neurogenetic studies may want to group the same sample of psychiatric subjects in different ways, for example, entity-based, subphenotype-based, and syndrome-based. This allows one to search for the specific neurobiological changes, that is, the intermediate phenotypes, related to the different clinico-phenotypic categorizations (see [65] for such strategy in catatonia) and to reveal which genes are relevant for and act how on behavior.

#### Beyond genetic correlates

The ultimate aim of neurogenetics is to map certain genes and their effects onto the brain’s neural activity and the respective behavior and clinical symptoms. The ideal scenario would be to find the sufficient genetic conditions
of the brain’s neural activity and the associated behavior and clinical symptoms. One could thus speak of ‘genetic correlates of brain and behavior’ (GCBB).

While the numerous investigations let to some insights into the linkage between genes, brain, and behavior, these are far weaker than initially expected in especially psychiatric disorders. Phenotypic variances remain unaccounted for by the genetic level that is generally described as ‘hidden heritability’ or ‘mystery of the missing heritability’ [27,38]. This gap in our current knowledge about the gene–brain–behavior connection may be due to empirical deficiencies in the choice of our genetic, neural, and clinical variables entering our experimental designs as described above.

In addition to such empirical constraints, one may also want to shed light on our current methodological strategy. Rather than targeting the sufficient conditions and thus the genetic correlates of brain and behavior, one may focus, at least at this point in time, more on the necessary non-sufficient conditions. These may create certain tendencies or susceptibilities (i.e. predispose) in the brain’s neural activity, as for instance in its resting state activity, to react to specific stimuli from the environment, that is, stimulus-induced activity, in particular ways. Since they only predispose rather than directly causing neural and behavioral changes, one may here speak of genetic susceptibilities or better genetic predispositions of brain and behavior (GPBB) rather than GCBB (Figure 1).

How are the GPBB mediated and manifest in the brain? Yet unknown forms of gene–environment (G × E interaction) and brain–environment interactions (B × E interaction) may impact the brain’s resting state activity and its spatial and temporal organization in yet unclear ways. Such genetic predispositions may lead to abnormalities in the resting state’s neural activity, that is, neural predisposition, to react neuronal and psychologically in depressogenic ways to specific events in the environment.

What is meant by the term neural predisposition? Analogous to a genetic predisposition in the case of genes, certain neural states in the brain, for example, especially its intrinsic activity, cause the respective person to be neurally liable and susceptible to react strongly to for instance certain life events. The concept of neural predisposition therefore refers to specific neuronal constellations in the brain’s intrinsic activity that are favorable to develop particular states and conditions. In other terms, a neural predisposition increases the probability of developing for instance MDD in the ‘right’ environmental context, for example, one that matches or corresponds to the neural predisposition. For instance, an abnormal resting state may be considered a neural predisposition to develop MDD that enhances, in yet unclear ways, the subjects’ susceptibility to particular life events like loss. While the resting state’s underlying neuro-genetic abnormalities may be regarded a GPBB of MDD [1,47].

The GPBB and the respective neural predispositions may in turn affect those genes, that is, the GCBB, and the stimulus-induced activities, that is, the neural correlates, that control the neural processing of particular sensory, emotional, and cognitive functions and consecutively the manifestation of clinical symptoms in MDD. Hence, complementing the current focus on GCBB by the GPBB

Figure 1

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<th>Environment (E): Stress and Trauma</th>
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<th>Genes (G): Candidate genes, Copy number variants, Polymorphisms</th>
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<td>Brain (B): Intrinsic activity, Low frequency fluctuations</td>
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Genetic and neural predispositions of brain and behavior. The figure illustrates the interaction between genes, environment and brain in a schematic way. Upper part: Genes are supposed to interact with the environment, gene–environment interaction, that is, G × E, via stress and life events. There is thus an interaction of environmental stimuli with genes, gene–stimulus interaction (left part). At the same time, and at least partly related, the brain also interacts with the environment, B × E interaction, via so-called stimulus-rest interaction (right part). Middle part: From the interaction with the environment, genetic predispositions of brain and behavior (GPBB) arise. They impact and constitute the brain’s intrinsic activity and its spatiotemporal organization and thus rest–rest interaction. The resting state activity may be considered by itself a neural predisposition for any subsequent neural activity during stimuli, that is, stimulus-induced activity. Lower part: The brain’s resting state activity ‘encounters’ life events and stimuli from the environment leading to stimulus-induced activity (left part). At the same time such stimulus-induced activity yields behavior and clinical symptoms via modulating sensory, affective, cognitive, and social functions of the brain (right part). The relationship between stimulus-induced activity and behavior/clinical symptoms is supposed to be mediated by genes mirroring the genetic correlates of brain and behavior (GCBB).
may narrow and ideally close the gap in our current neurogenetic knowledge. This may ultimately solve the ‘mystery of the missing heritability’ in psychiatric disorders like MDD.

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References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


This is an excellent review about recent findings in the neuroimaging and genetics of depression. The authors discuss the genes for the different biochemical and their relation to imaging findings in depression.


This is an overview of the recent findings on serotonin transporter and its impact on social abnormalities and emotion. Both authors are leading in his domain of serotonin transporter.


This is an impressive paper about the effects of deep brain stimulation from Helen Mayberg and colleague who introduced this method of treatment. Depression is here characterized as a disorder of neuronal regulation.


This is one of the first studies that demonstrated resting state abnormalities in the anterior cortical midline regions in depression and how that relates to clinical symptoms.


This is an excellent review about the neuronal features, its structural and functional connectivity, its neurosychological characterization, and its role in deep brain stimulation of the subgenual anterior cingulated cortex.


This is a first paper showing the direct interaction neural and endocrine activity and its genetic and social modulation. An excellent paper showing how stress impacts genetic, endocrine, and neural function.


The paper demonstrates how the genes underlying the BNDF pathway impact cognition and environment. This is a paradigmatic way of how interaction between genes, cognition, and environment can be investigated.


An impressive review paper about the future of fMRI in relation to genetics from one of the leading authors in the field.


An impressive study demonstrating linkage between hormonal-receptor activity and neural activity during emotional stimulation. This further underscores the close and intricate relationship between stress, cortisol and emotion.


The paper demonstrates recent data on the relevance of the social environment for the genetic make-up and the neuronal mechanisms of the gene-environment interaction.


[Epub ahead of print]. A recent study showing that the neural activity in the default-mode network is mediated by the DRD2 genotype modification and striatal receptor binding. This is an impressive demonstration of how different imaging techniques can be combined with genetic approaches.


