

Molecular Genetic Aspects of Personality

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1 Introduction

Personality psychology and behavior genetics share a common theme: the investigation of given interindividual differences. Because genetic variations belong to the most powerful influences on behavioral dispositions and human behavior, behavior genetics can be seen as one of the core areas of differential and personality psychology. The more we know about genetic mechanisms underlying individual differences, the more promising it will be to look for neurobiological pathways, which explain individual differences in human behavior and which may be generalized to explanations of the behavior of all individuals (the “modal” person).

Modern behavior genetics is primarily characterized by three basic questions, which coevally delineate the main fields of this research area:

- 1 Which kinds of behavior and behavior dispositions are influenced, and to what extent, by genetic factors and, respectively, by environmental factors? (*quantitative behavior genetics*)
- 2 What specific genes are important for specific kinds of behavioral dispositions or traits? (*molecular behavior genetics*)
- 3 How and by what mechanisms and behavior genetic pathways do genes impact on behavior? (*functional genomics*)

Important foundations of genetics have already been realized in the middle of the nineteenth century (Mendel, Galton). Its further development ran in orderly ways for a long time. At the beginning of the twentieth century Mendel’s laws were rediscovered, twin and adoption studies developed, and the extension to complex traits with multiple genetic and environmental influences began with Fisher (e.g. Fisher,

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1918). In the second half of the twentieth century the detection of the structure of DNA and the detection of the genetic code were milestones of the further development of molecular genetics. The vast decoding of the genome at the beginning of twenty-first century marks the apex of this development. A breathtaking development and new, powerful tools characterize present molecular genetics: linkage analysis, positional cloning, and candidate gene studies dominated molecular genetic research in the nineties; genome-wide association analyses, genome-wide sequencing, endophenotype analyses, epigenetics, transcriptomics, and proteomics are going to mark the research of the coming decade.

With the establishment of differential psychology at the beginning of the past century, the nearest relative of behavior genetics arose early. This chapter is intended to provide a current overview of the *molecular genetics* approach of behavior genetics. In the following pages we will introduce the foundations and methods of the molecular genetic approach to the study of individual differences (Section 2). Then we will give an overview over theories and models in personality psychology, which provide one necessary basis for deductive candidate gene studies (Section 3). In the main part of our overview (Sections 4 and 5), we will delineate important findings on genetic variations and environmental factors influencing personality. The last section finally outlines current developments and future directions in molecular genetic approaches.

2 Foundations and Methods

This section will introduce basic concepts and methods of the molecular genetics of individual differences. First, conceptual issues (what are genetic polymorphisms, whether and how they impact on behavior) will be summarized shortly to further the understanding of methodological approaches of molecular genetics, i.e., how can genetic polymorphisms be studied and linked to individual differences; these approaches will be outlined in the second part of the section, where the main focus will be on association studies.

2.1 Genes, genetic variations, and their potential impact on behavior

Our genes—strands of deoxyribonucleic acid (DNA) located on 23 pairs of chromosomes in the cell nucleus—code for proteins, e.g. enzymes responsible for the synthesis or degradation of certain neurotransmitters. A gene complex consists not only of coding regions or exons—that is, sequences of so-called triplets of nucleotide bases (adenine, thymine, guanine, and cytosine), which code for certain amino acids and their sequence in the final protein—but also of non-coding regions or introns, which can have some regulatory function, and finally of transcriptional control regions, or promoters, located upstream of a gene. These promoters have a regulatory function and are important regulators of the transcription of a gene.

If, on the basis of cellular mechanisms, a signal is generated that more of a given protein is needed, then transcription factors bind to certain recognition sites within the gene promoters. This allows a ribonucleic acid (RNA) polymerase protein complex

to bind to the DNA and to start the gene transcription at the so-called start codon (i.e. the nucleotide sequence ATG). The DNA sequence is subsequently transcribed into RNA via an assembly of nucleotide bases, according to the DNA template sequence. Afterwards, during the so-called splicing, messenger RNA (mRNA) is generated from the RNA: in other words, intronic information is cut and only exonic information is retained. Then the mRNA is transferred to the ribosomes for translation, that is, for the mRNA-code-based assembly of amino acids into the final protein.

With the exception of the sex chromosomes of males, each gene has a corresponding gene on the partner chromosome, one from each parent. Such corresponding gene variants are called alleles. These alleles can be identical or can differ with regard to their nucleotide sequence. Importantly, the term “allele” is also used to refer to interindividual variation in one gene’s nucleotide sequence, and such variation is frequent throughout the genome. Genetic variation can be due to errors during DNA replication or to external factors, and it can, but must not, have an impact on the function of the gene product—the protein. If alterations of the nucleotide sequence are found in more than 1 percent of a population, the term “polymorphism” should be used; otherwise the term “mutation” is commonly used to denote a rare genetic variation.

There are different kinds of possible genetic variations. First, single nucleotides can be substituted by another nucleotide. These *single-nucleotide polymorphisms* (SNPs) may affect a gene product’s function if they are located in exonic regions and may change the code for a given amino acid. As already mentioned, three nucleotide bases form one coding element, for example AAC codes for the amino acid asparagine. If, due to some single nucleotide substitution, the code is changed to AAT, then the gene product will still be the same (a so-called silent variation), as AAT also codes for asparagine. If, however, the nucleotide sequence is changed to AAA or AAG, then the amino acid lysin is incorporated into the protein chain at the respective site (a missense variation), and this can affect the protein’s structure, and hence function, which ultimately may affect some brain mechanism underlying a behavioral trait. SNPs can affect the function of a gene product also if they destroy or create a recognition site for transcription factors in the gene promoter, or if they reside in such intronic gene regions, which may have regulatory functions.

Second, nucleotides can be inserted into, or deleted from, a given sequence (*Ins/Del polymorphisms*), and, third, a certain nucleotide sequence can be multiplied, resulting in *repeat polymorphisms* (e.g. so-called variable number of tandem repeats, VNTR). Again, on the basis of the location of such variation in exons, introns, or promoters, changes in the function of a gene product are possible, but not mandatory.

The functional significance of a given genetic variation can be examined *in vitro*, for instance via expression studies using model cells, but also *in vivo*, for instance via post mortem expression studies, or finally *in silico*, on the basis of database-driven information on whether, say, a given genetic variation creates or destroys a transcription factor recognition site. The demonstration of the actual or likely functional significance of a genetic variation provides a reasonable basis for investigations into the role of this genetic variation in the modulation of individual differences in behavioral phenotypes. Then we can move on and follow one of the approaches outlined in what follows, to relate genetic to phenotypic variation.

2.2 Molecular genetic approaches and methods

As stated above, genes do not code for behavior, but for proteins. How, then, can behavioral differences be associated with genetic variation? The logic is as follows: functional alteration in cellular mechanisms (i.e. neurotransmitter synthesis) may affect more global functions (e.g. the balance of the function of a given neurotransmitter within a certain neuronal circuit) and ultimately brain systems subserving complex behavior (e.g. systems involved in the processing of emotional stimuli), thereby impacting on individual differences in behavioral traits (e.g. affectivity) and vulnerability to psychopathology (e.g. depression). Despite this unifying logic, there are two, or rather three ways to close the gap between the two ends of the behavioral genetic pathway.

First, we can start at the behavioral level. We gather theory- or experience-based information on putative biological substrates of some behavioral trait such as a temperament dimension, or a cognitive function including associated psychological disorders. We then identify genetic variations, which are likely to impact on these biological substrates, and finally we associate these genetic variations with individual differences in the behavioral traits under question, for example via examination of mean differences of trait expressions between carriers of different variants of our pre-selected genetic polymorphisms. This top-down strategy is the so-called *candidate gene approach*, and it has been followed in the vast majority of molecular genetic investigations of individual differences so far.

Second, we can start with the observation of some gene exhibiting a high degree of polymorphism. Here, the very existence of such polymorphism seems reasonably due to some evolutionary fitness gain associated with certain forms of this variation. We then need to identify the biological mechanisms which are impacted by this genetic variation, and ultimately we may arrive at some behavioral trait which is likely to be influenced by this biological mechanism, and thus likely to be associated with the genetic variation under discussion. This bottom-up approach could be termed *candidate phenotype approach*, and it has been pursued much less frequently than the candidate gene approach.

Third, while the two above-mentioned approaches are deductive and hypothesis-testing in nature, we can also follow an inductive and *hypothesis-generating* approach and use as much information on genetic variation as possible in order to identify so far unknown genetic factors presumably impacting on behavioral differences. Here we can use so-called genome-wide association studies (see Section 6.1) and examine hundreds of thousands of polymorphic gene variants, spread across the whole genome, with respect to their role as marker variables for DNA regions possibly involved in individual differences in one or more of the behavioral traits under investigation. In the near future, we might also be able to examine every single data point of individual genomes with respect to its role in modulating individual differences in behavioral traits. This inductive *genome-wide approach* certainly has some appeal, but it also has several limitations, which will be outlined below (see Section 6.1).

Whatever approach we use, we need to determine both the genotypic and the phenotypic status of our subjects in order to perform association tests using, say, chi-square tests (in the case of binary traits such as the presence or absence of a

disorder) or analyses of variance (in the case of a continuous trait such as a personality dimension). To genotype our subjects, individual DNA needs to be extracted from cell samples such as blood cells, or more conveniently from buccal cells or saliva, and to be subjected to a method which enables us to determine which variants of a given polymorphism can be identified in a given individual. There are numerous ways to achieve this, and even to mention and briefly describe all of them would require several further sections. Therefore only the simplest method shall be described shortly in what follows: namely polymerase chain reaction (PCR) followed by electrophoresis.

PCR allows us to amplify segments of the DNA, which harbor a polymorphism of interest via “tagging” this segment by using so-called primers (i.e. short sequences of nucleotide bases, which match the nucleotide sequences flanking the segment of interest) and repeated duplication of the segment until a critical number of copies is achieved. Electrophoresis is used to determine the length of the amplified segments: the PCR products are tagged with an UV-marker and applied to a porous carrier substance, for instance an agarose gel. After application of voltage, the negatively charged DNA travels through the pores of the carrier substance, shorter DNA segments travelling faster. After a while one can differentiate between segments of different length by photographing the DNA on the carrier substance under UV light. In the case of repeat length polymorphisms, the fragment length directly informs about the genotype (e.g. a fragment of 300 base pairs [bp] in length might constitute a double repeat of a sequence of 150 bp, while a sequence of 450 bp identifies this fragment as a triple repeat). In the case of SNPs or Ins/Del polymorphisms, an intermediate step becomes necessary: before electrophoresis, an enzyme is applied to the PCR product, which cuts the DNA if it recognizes a certain nucleotide sequence. The presence or absence of a given nucleotide base of a SNP, or an insertion or deletion, respectively, might create or delete such a recognition site, and hence the application of the enzyme results in cut or uncut fragments, which differ in length and may be distinguished after electrophoresis (e.g. the substitution of an A to a G at position 200 of a fragment of 600 bp in length might create a recognition site for a cutting enzyme; a carrier of two A alleles would therefore be identified by two shorter—cut—fragments, whereas a carrier of two G alleles would be identified by two long—uncut—fragments, and a carrier of an A/G genotype would be identified by one short and one long fragment). Hence, on the basis of PCR/electrophoresis, we can determine which variants of genetic polymorphisms are found in a given individual and can link this information with phenotypic measures.

To “phenotype” our subjects, we need to determine behavioral traits which, depending on our research topic, may be disease status, dimensions of cognitive functioning, or personality traits. Here we can refer to diagnostic criteria for mental disorders using the classifications provided in the *ICD-10* (World Health Organization, 1992) or in the *DSM* (American Psychiatric Association, 2000); to cognitive psychological theories and their operationalizations, in other words, to experimental paradigms; or to personality theories and their operationalizations, that is, self- and peer report questionnaires. The theories underlying the latter phenotypic measures will be outlined in what follows, so as to provide a basis for the assessment of the potential for top-down candidate gene approaches.

3 Candidate Gene Approaches: Theories Informing about Gene–Trait Associations

As outlined above, the effects of genetic variance are not expressed directly at the level of behavior. They are mediated by molecular and cellular effects on neural mechanisms and processes underlying behavior and behavioral dispositions or phenotypes, i.e. traits. Neurobiological theories of personality, explaining individual differences in emotional and cognitive behavior, inform about underlying neural processes and mechanisms, which offer hints as to the genetic influences possibly involved (*forward genetics*; Seyffert, 1998). Conversely, known genetic variation, e.g. of the serotonergic system, may provide a basis to identify neural processes and mechanisms associated with phenotypic individual differences yet to be detected (*reverse genetics*). This section gives an overview of relevant theoretical models in personality psychology, which have provided one necessary basis to identify candidate genes, thus enabling deductive candidate gene studies.

We will shortly describe in detail Eysenck's biopsychological PEN-theory as the origin of this new kind of neurobiological theorizing in personality psychology; the reinforcement sensitivity theory (Gray); the five dimensional model of personality (Depue); the biosocial theory of personality (Cloninger); as well as further approaches (Zuckerman, Davidson, Panksepp). We will close with an investigation of the presumptive relations of these theories to the five-factor model (FFM or "Big Five"), and we will discuss suggestions for integrating these models with respect to the question of how they can aid molecular genetic research into individual differences.

3.1 Correlational and biopsychological trait theories

Eysenck's PEN-theory (Eysenck, 1967, 1981, 1997; Eysenck & Eysenck, 1985) was the first of the early influential models of personality (Cattell, Guilford) which transcended the limited potential of purely correlational systems by systematically specifying the causal neurobiological mechanisms underlying individual differences. While correlational theories only allow to describe, diagnose, and predict individual differences, causal theories allow to *explain* individual differences and to answer questions like: "Why do extraverts frequent societal situations?" (Brocke, 2000). In addition, Eysenck's paradigmatic kind of theory systematically combined a correlational description of the personality types—extraversion (E), neuroticism (N) and psychoticism (P) (the descriptive personality theory)—with a large body of neurobiological causal component theories explaining the behavioral characteristics of these types (the arousal/activation theory and its component theories). Further, this theory has been conceived as a twofold hierarchical system with a hierarchy of correlational assumptions describing the three "superfactors," or types E, N, and P, and 27 more specific factors ("traits") on the one hand, and a hierarchy of neurobiological assumptions on the mechanisms underlying these personality factors on the other hand (for a systematic description, see Brocke & Battman, 1992; Brocke, Hennig, & Netter, 2004). Thus the theory offers a rich body of information and a basis for the identification of genes potentially associated with the traits or phenotypes of the model.

In the neurobiological part of the PEN-theory, Eysenck focused on the activity of the ascending reticular activating system (ARAS or reticulo-cortical circuit), the activation of which he called *arousal*. He postulated the differential reactivity of this system, differential *arousability*, as the basis of extraversion. The activity of the reticulo-limbic circuitry was labeled *activation*, and he hypothesized that differential *activation thresholds* are the basis of neuroticism. He postulated that extraverts have a lower arousability of the reticulo-cortical circuit than introverts, and therefore they seek more stimulating activities and sensations in order to achieve their preferred level of arousal. Neurotics are more easily *activated* by emotion-inducing stimuli (reticulo-limbic circuit) and, because of the association of the two circuits, they get eventually more *aroused* (reticulo-cortical circuit) than emotionally stable individuals are. The theory does not specify a systematic biological model of psychoticism, but Eysenck postulated a negative association of psychoticism with the serotonergic system and a positive association with dopaminergic function (Eysenck, 1997; Eysenck & Eysenck, 1985).

Eysenck's theory is of central importance as an origin of the new neurobiological personality theories integrating causal and correlational components. The valid parts of the theory offer a basis to identify candidate genes, thus enabling deductive candidate gene studies. However, parts of it are no longer in accordance with latest findings of neuroscience and have to be modified or adjusted, as happened with the concept of "unspecific arousal" and the underlying activity of the ascending reticular activating system (cf. Fischer, Langner, Birbaumer, & Brocke, 2008). Other parts have to be crucially revised and further developed, as is described below (Gray, Depue, Cloninger).

3.2 Revised reinforcement sensitivity theory (rRST)

Jeffrey Gray worked in close connection with Eysenck's approach, criticizing, modifying, and basically enhancing his main assumptions (Gray, 1982). He developed a conceptual nervous system encompassing three components. The behavioral inhibition system (BIS) is sensitive to conditioned aversive stimuli, to omission or termination of expected reward, and to a class of diverse inputs, including extreme novelty, high intensity stimuli, and innate fear stimuli (blood or snakes). The behavioral approach system (BAS) is postulated to be sensitive to conditioned appetitive stimuli and to the termination or omission of signals of punishment; and the fight-flight system (FFS) is sensitive to unconditioned aversive stimuli (innately painful stimuli). In a substantially revised version, Gray and McNaughton(2000) updated and elaborated the preceding version of Gray's theory and made different predictions in some essential respects.

In the revised version of the RST (rRST; for details, see Luke Smillie's chapter in this volume), the former FFS includes "freezing" and is now called the "fight-flight-freeze" system (FFFS). It is responsible for reactions to *all* aversive stimuli, conditioned and unconditioned, and leads to active avoidance or attempted elimination (panic, flight, or fight). The BIS was the most modified system; it is now conceived of as being responsible for the resolution of goal conflict in general, for instance it responds to stimuli which arouse desire, but at the same time contain potential threat

(approach–avoidance). Such conflicts may be induced by simultaneously activating the FFFS and the BAS, whereas the BIS acts as a detector of the resulting approach–avoidance conflict. Avoidance–avoidance and approach–approach conflicts can also trigger the BIS. Activation of this system produces vigilance and passive avoidance, and is involved in processes leading to anxiety-formation. The BAS is now responsible for reactions to *all* appetitive stimuli, conditioned and unconditioned, and produces approach behavior.

The neural instantiation of the BAS is postulated to be in the mesolimbic dopaminergic circuit; the neural basis of the BIS is postulated to be in the septo-hippocampal system and the amygdala; and the FFFS is linked to the amygdala, hypothalamus, and periaqueductal gray. Originally, BIS and BAS reactivity were associated with anxiety and impulsivity, respectively; hence both traits were described as 30-degree rotations from neuroticism and extraversion. Meanwhile, along with the revision of the RST, Gray and McNaughton described neuroticism as sensitivity to general threat, associated with both BIS and FFFS activity. In addition, extraversion and not impulsivity is increasingly seen as being associated with BAS reactivity (e.g. Corr, 2009; Smillie, Pickering, & Jackson, 2006). Together with the problem that former measures of the RST traits (Carver & White, 1994; Torrubia, Ávila, Moltó, & Caser, 2001) do not represent the revised functions of the three neurobiological systems, the psychometric basis of the rRST is the weakest part of this theory.

3.3 Cloninger's biosocial theory of personality

Modifying and enhancing central concepts of the three-system RST, C. Robert Cloninger (1987) developed a theory which was similarly based on three distinct neurobiological systems underlying three basic personality traits: novelty-seeking (NS), harm avoidance (HA), and reward dependence (RD). In a later version of his theory, he included four further personality traits: persistence, cooperativeness, self-directedness, and self-transcendence. He postulated that the first four of the seven traits have a biological basis and should strongly be genetically influenced (being dimensions of the “temperament”) and the latter three are primarily formed by experience and not by genes (they are dimensions of “character”). With regard to the intention to identify candidate genes influencing phenotypic variation, we focus on the neurobiologically founded temperamental traits. To measure the traits of his model, Cloninger developed the Tridimensional Personality Questionnaire (TPQ; Cloninger, Svrakic, & Przybeck, 1991) and later on the Temperament and Character Inventory (TCI; Cloninger, Przybeck, Svrakic, & Wetzels, 1994).

The three biological systems underlying the temperamental traits are activated by cues of novelty (behavioral activation system), danger (behavioral inhibition system) and reward (behavioral maintenance system) and produce approach and avoidance behavior (Cloninger, Svrakic, & Przybeck, 1993). They are primarily mediated by an individual neurotransmitter system. Cloninger postulated that the serotonergic system is associated with HA, the dopaminergic system with NS, and the norepinephrine system with RD.

Because of this one-trait–one-neurotransmitter hypothesis, the biosocial theory of personality became very popular as a basis for deductive candidate gene studies.

Variation of genes modulating an individual neurotransmitter system were hypothesized as candidate genes for the temperamental trait influenced by the respective neurotransmitter. However, this assumption, as well as the postulated seven-factor structure, could not be unambiguously confirmed; and there is some contradicting evidence (DeYoung & Gray, 2009).

3.4 Depue's five dimensional model of personality

Depue started the development of his theory with a neurobiological differentiation of two kinds of the complex extraversion trait. He described agentic extraversion as primarily dopaminergic-modulated, and affiliative extraversion as modulated by opioids and peptides like oxytocin (Depue & Collins, 1999). Depue's theory in its recent state postulates five dimensional traits (Depue & Lenzenweger, 2005): (1) *agentic extraversion*, based on dopamine facilitation of the incentive of reward motivation; (2) *affiliation*, based on mu-opiate mediation of appetitive and consumatory reward processes; (3) *anxiety or neuroticism*, based on the activity of corticotrophin-releasing hormone in the limbic structures, in the bed nucleus of the stria terminalis (BNST), and in the rostral medulla; (4) *fear*, based on amygdala activity responding to particular localized threat, and (5) *non-affective constraint*, based on serotonergic modulation of the expression of other emotional traits.

The differentiation of neuroticism/anxiety from fear was proposed (White & Depue, 1999) concurrently with the differentiation of agentic extraversion and affiliative extraversion (Depue & Collins, 1999). In the final version of his approach, Depue dropped "extraversion" from the label of the latter trait and he presented a theory of "affiliative bonding" (Depue & Morrone-Strupinski, 2005). His most recent empirical work focuses on the interplay between pharmacologically facilitated neurotransmitters and neuropeptides and psychological processes related to temperament, with the goal of understanding differences in the behavioral expression of these traits.

Depue used the Multidimensional Personality Questionnaire (Tellegen & Waller, 1992) to measure his five dimensions: the MPQ scales of social closeness for affiliation, social potency for agentic extraversion, stress reaction for anxiety, and MPQ harm avoidance for fear. Finally he used MPQ impulsivity vs. control to represent non-affective control.

3.5 Further approaches and an integration

Zuckerman (1994, 2005) has provided a rich body of knowledge of biosocial personality psychology. He developed a (correlational) five-factor model of personality, the *Alternative Five*, describing the personality factors of sociability, neuroticism-anxiety, aggression-hostility, impulsive sensation-seeking, and activity (Zuckerman, Kuhlman, Joireman, Teta, & Kraft, 1993). Starting in the sixties and later on in parallel with work on his correlational model, Zuckerman developed a biosocial theory as a basis for his model, and primarily for sensation-seeking (Zuckerman, 2005). Contrary to Cloninger's approach, his biosocial theory is characterized by the assumption that neurobiological traits are mediated by multiple biological systems,

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rather than by individual neurotransmitter systems. Impulsive sensation-seeking is for example modulated by dopamine, serotonin, and norepinephrine, as well as by gonadal hormones and further mechanisms. A second characteristic of his approach is the view that only those personality traits which have a biological basis and substantial heritability can be seen as basic personality dimensions (Zuckerman, 2005, 1993). A third important feature of his approach is the hierarchical structure of the theory (Zuckerman, 1990; Brocke, 2004), a multi-level approach encompassing seven levels from genes to behavior.

Among further biopsychological theories of personality, two more approaches should be mentioned. Jaak Panksepp developed a neurobiological personality theory comprising six traits. He labelled them playfulness, seeking, caring, fear, anger, and sadness, and he postulated that they were influenced by six neurally based networks or emotional systems (Panksepp, 1998). Additionally, he developed an inventory for the psychometric operationalization of his neurobiological traits (Affective Neuroscience Personality Scales, ANPS; Davis, Panksepp & Normansell, 2003). Thus his model exhibits the same structure as the other neurobiological theories, containing a descriptive, psychometric, and mostly correlational component and an hypothetically causal biopsychological component.

On the basis of neuropsychological and psychophysiological findings, Richard J. Davidson postulated two separate brain systems, located in the right and left hemisphere, respectively, which are basically involved in behavior regulation (Davidson, 1992). The system located in the left prefrontal area is part of a motivational system and is responsible for approach behavior. Apart from the left prefrontal cortex, this system comprises subcortical structures, especially the nucleus accumbens, and dopamine is involved in the modulation of approach behavior. Davidson postulated a complementary motivational system, located in the right prefrontal cortex and in limbic structures like the amygdala and hypothalamus, which is responsible for retreat behavior. Davidson assumes that not all individuals show a symmetric activity of both systems, but rather tend to exhibit either a left or right prefrontal base activity of the cortex. This frontal asymmetry is assumed to be a stable disposition and to be ascertainable by indicators of the spontaneous EEG. Individuals with a relatively left frontal asymmetry show a greater sensitivity to approach behavior and exhibit a marked positive emotionality. Individuals with a relatively right frontal asymmetry are predisposed to exhibiting retreat behavior and marked negative emotionality. The emotional traits of positive and negative emotionality corresponding to the respective frontal asymmetry are often measured with the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988).

The personality theories described above show considerable overlap and shared explanations. Not least for the purpose of obtaining an informative basis for the identification of candidate genes associated with phenotypic variation, an integration of these theories seems to be attractive. However, one has to be careful to avoid premature structuring of the field, which lacks sufficient evidence.

With respect to the goal of identifying candidate genes associated with phenotypic variation, a suggestion made by Revelle (1995) looks especially promising. Revelle describes three basic behavioral dimensions: approach, avoidance, and fight-flight behavior. These behavioral dimensions widely correspond to characteristic activity in

the neurotransmitter systems: dopamine (approach behavior; e.g. extraversion, sensation seeking, novelty seeking); serotonin and noradrenaline (avoidance behavior; e.g. anxiety, neuroticism, negative emotionality); and serotonin, noradrenaline, and gamma-aminobutyric acid (fight-flight behavior; e.g. fear). Revelle's typology as a basis for integration might be helpful in generating suggestions for candidate genes. However, the presumptive associations with individual psychometric trait concepts still have to stand the test (cf. Sen et al., 2004).

DeYoung and others made the suggestion to translate the results from the models described above "into a single common language" (DeYoung & Gray, 2009) relating each model to the five-factor model of personality (FFM or Big Five; Costa & McCrae, 1992; Digman, 1990; Goldberg, 1990). However, there has been no sound authentic biological basis for the Big Five for long, which made the translation difficult. To import the neurobiological systems underlying the personality dimension of the theories described above may again be helpful in generating suggestions for candidate genes; however, it may again risk premature integration.

Only recently has a systematic, though preliminary, effort been undertaken to develop a biological basis for the FFM. Questioning the independence of the five domains (extraversion, neuroticism, agreeableness, conscientiousness, openness), some research results showed slight intercorrelations and demonstrated a higher-order factor structure (DeYoung, 2006; Jang et al., 2006). Neuroticism, agreeableness, and conscientiousness formed one higher trait, named α or *stability*, and extraversion and openness formed another, named β or *plasticity*. Jang et al. (2006) provided data suggesting that the two higher-order traits are genetically influenced. DeYoung and Gray (DeYoung 2006; DeYoung & Gray, 2008) and Yamagata et al. (2006) suggest that stability is related to serotonin and plasticity may be related to dopamine. DeYoung and Gray (2008) see the identification of dopamine and serotonin as presumptive biological substrates for the higher order traits as the beginning of a psychobiological model for the (hierarchical) FFM. In the context of a literature review, they generate hypotheses about biological substrates for the domains, substrates that would be unique for the individual domains, and they are looking for shared substrates for the higher-order traits. Thereby they primarily inspect the above-described biopsychological theories and additional material.

4 Molecular Genetic Main Effects

In this section we will sketch paradigmatic evidence on the potential role of genetic variation (1) in modulating personality traits, exemplified by the impact of genetic variation in serotonin transporter function on individual differences in anxiety- and depression-related personality traits; (2) in the development of psychopathology, again, by focussing on genetic variation of serotonin transporter function and its putative associations with affective and anxiety disorders; and (3) in modulating psychophysiological correlates of personality and psychopathology, e.g. genotypic differences in fMRI-parameters of emotional processing.

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4.1 Personality traits

The personality theories outlined in Section 3 suggest the existence of a general personality dimension of negative emotionality, comprising aspects of neuroticism *sensu* Costa and McCrae, of behavioral inhibition *sensu* Gray, of harm avoidance *sensu* Cloninger, and of related constructs. Taken together, negative emotionality can be conceptualized as a stable and heritable sensitivity to aversive stimuli (Clark, Watson, & Mineka, 1994). Given that negative emotionality can be viewed as a dimension of the vulnerability toward developing anxiety and affective disorders (Clark et al., 1994; Kendler, Gatz, Gardner, & Pedersen, 2006; Ormel, Oldehinkel, & Vollebergh, 2004), and given that negative emotionality shows high genetic correlations with these disorders (Carey & DiLalla, 1994), we may view anxiety and depression as extremes of normal variation in negative emotionality.

Hence, genetic variation impacting on the biological mechanisms involved in the development of affective and anxiety disorders may also modulate individual differences in the vulnerability dimension of negative emotionality. If we take into account that certain chemical compounds—like selective serotonin reuptake inhibitors (SSRIs)—can be used successfully to treat psychological conditions such as anxiety disorders or depression (see, e.g. Nemeroff & Owens, 2002), some variation in the gene encoding the target site for SSRI action, the serotonin transporter, is likely to affect a biological mechanism involved in the vulnerability to develop these disorders. Therefore an association between genetic variation of serotonin transporter function and negative emotionality seems plausible.

This logic was applied in a seminal study by Lesch and colleagues (Lesch et al., 1996). The authors focussed on a polymorphic sequence in the promotor of the serotonin transporter gene, previously detected by that group and termed serotonin (5-HT) transporter (5-HTT) linked polymorphic region (5-HTTLPR; Heils et al., 1996). 5-HTTLPR is an insertion/deletion polymorphism with a long (L) variant comprising 16 copies of a 20–23 base pair repeat sequence and a short (S) variant comprising 14 copies. Among Caucasians, the frequencies of the L and S alleles are about 0.60, and 0.40, respectively (Heils et al., 1996), although allele frequencies vary across different populations (Gelernter, Cubells, Kidd, Pakstis, & Kidd, 1999). The S allele is associated with lower transcriptional efficiency of the 5-HTT gene, and hence with lower levels of serotonin uptake (Heils et al., 1996; Lesch et al., 1996).

Interestingly, Lesch and colleagues (Lesch et al., 1996) observed carriers of the S allele to exhibit significantly higher scores in neuroticism as measured using the NEO-PI-R. This effect explained only 2–4 percent of the variance in neuroticism—an effect size which is typical for association studies of complex traits, because such traits are likely to be influenced by a large number of genes, which additively or interactively impact on a given trait. Nevertheless, such small effects can be of high value for the understanding of the neurogenetic underpinnings of behavioral differences, given that they are biologically plausible and can be replicated.

Concerning the biological plausibility of the association between the 5-HTTLPR S allele and neuroticism, this result might at first glance seem counterintuitive, as carriers of a gene variant associated with lower serotonin transporter function showed significantly higher scores in a vulnerability factor for affective and anxiety disorders,

which can effectively be treated with SSRIs that inhibit serotonin transporter function. Here we must take into account that a genetic variation may impact on physiological processes in the long term, perhaps via a role during critical developmental phases. It seems likely that a genetically mediated reduction in serotonin transporter function might result in higher serotonin levels during critical developmental phases, which in turn might prompt counteracting inhibitory processes with regard to serotonin synthesis and release via the action of serotonin autoreceptors. This might ultimately result in a lower serotonin release and concentration in the synaptic cleft, which then needs to be raised using SSRIs and which may impact on the re-regulation of serotonin turnover and serotonin neuromodulation. Of course, alternative explanations exist.

Concerning the replicability of this association, it has to be noted that the finding of Lesch and colleagues has been replicated in a number of studies, mostly by using NEO-PI-R neuroticism or TPQ harm avoidance to assess variation in negative emotionality. While there are also conflicting results and non-replications, current meta-analyses point to a replicable effect of 5-HTTLPR variation of negative emotionality, given that negative emotionality is assessed by using the NEO-PI-R (Schinka, Busch, & Robichaux-Keene, 2004; Sen, Burmeister & Ghosh, 2004; see, however, Munafò, Clark, & Flint, 2005). These meta-analytic findings may indicate that the behavioral phenotype impacted by 5-HTTLPR-mediated variation in the function of brain systems may be more closely related to the five-factor model conceptualization of negative emotionality than to Cloninger's conceptualization of harm avoidance. Another possible reason for the inconsistency of the present findings can be seen in the fact that a recently discovered A to G single nucleotide substitution within the region designated as 5-HTTLPR impairs the transcriptional efficiency of the L allele (Hu et al., 2005), with only carriers of the common L_A/L_A genotype exhibiting high 5-HTT gene transcription. Therefore, in earlier studies, several individuals with the rare L_G variant may indeed have shown comparably low levels of 5-HTT transcription as carriers of the S allele.

4.2 Psychopathology

Given the association between the 5-HTTLPR S allele and a vulnerability dimension for the development of affective and anxiety disorders, it seems plausible that the 5-HTTLPR S allele should also be over-represented in individuals diagnosed with these disorders. Intriguingly, however, evidence from meta-analyses suggests small positive associations of the S allele with bipolar disorder and suicidal behavior, but not with depression itself (Levinson, 2006). Similarly inconclusive is the evidence concerning associations of 5-HTTLPR with anxiety-related disorders such as panic disorders (Maron & Shlik, 2006) or obsessive-compulsive disorder (Bloch et al., 2008).

This inconclusive evidence may in part be due, again, to methodological differences between studies. It may, however, also be explained by the possibility that common genetic variants such as 5-HTTLPR may imply some predisposition to develop psychopathology, but only in interaction with other genetic or environmental factors such as adverse life events. Before this issue will be covered in more detail in

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Section 5, we will close the present one with exciting findings concerning the neurobiological underpinnings of the role of 5-HTTLPR in the modulation of information-processing networks assumed to be disturbed in anxiety and depression in order to show that, despite inconclusive evidence on a given polymorphism's role in modulating *phenotypic* behavioral expressions, we might be able to gather more consistent evidence at a so-called *endophenotypic* level.

4.3 Endophenotypes

The term *endophenotype*, reintroduced by Gottesman and Gould (2003), refers to some measure of individual differences at a more basic level, for instance the behavioral, cognitive, neurophysiological, biochemical, endocrinological, or neuroanatomical level, which is assumed to causally impact, on or at least to correlate with, a given phenotype—such as a disorder or a personality trait. Within the context of the present example, an endophenotype of negative emotionality as a vulnerability factor for the development of affective and anxiety disorders could, say, be a neurobiological substrate relevant for the processing of aversive stimuli. Promising endophenotypes for negative emotionality therefore are measures of the function of amygdala-relayed cortico-subcortical circuits, as the amygdala can be regarded as a key structure in emotional processing, especially of aversive events.

Following this logic, a seminal functional magnetic imaging (fMRI) study by Hariri and colleagues (Hariri et al., 2002) demonstrated that carriers of the 5-HTTLPR S allele exhibited a higher neuronal activation in the amygdala in response to negative facial expressions. This finding has been replicated and extended by showing that 5-HTTLPR genotype also impacts on the functional connectivity between the amygdala and ventromedial prefrontal and anterior cingulate regions (Heinz et al., 2005; Pezawas et al., 2005). Hence, the 5-HTTLPR S allele seems to play a role in amygdala responses to aversive stimuli, which may be regarded as one factor underlying the higher scores in negative emotionality observed for carriers of the S allele (see above). Thus this evidence points to a biologically plausible mechanism, which mediates between variation at the 5-HTT gene locus and behavioral expressions of a heightened sensitivity to aversive events, being the core feature of negative emotionality.

Another example of an endophenotype of negative emotionality is the startle reflex, that is, the reflexory (or reflex) response of an organism to sudden high-intensity stimulation, which in itself may be of aversive nature. In our own studies (Brocke et al., 2006; Armbruster et al., 2009), we were able to show that 5-HTTLPR S allele carriers exhibit an elevated startle response. Hence this evidence suggests that, even at the level of basic reflexes, genetic variation in serotonin transporter function impacts on individual differences in responses to aversive events.

5 Gene–Gene and Gene–Environment Interactions, and Pleiotropic Gene Effects

Given that a main effect of a genetic variation on some biological substrate—e.g. the 5-HTTLPR-mediated heightened amygdala response, or the elevated startle

reflex to aversive stimulation—has adverse behavioral consequences, such as the development of a psychopathology, the question arises why this variation has not been removed from the gene pool during evolution, due the resulting reduction in fitness.

The present section is therefore devoted to solutions to the evolutionary puzzle of the existence of genetic variations potentially predisposing to psychopathology, and consequently to fitness reductions. One promising answer to this puzzle is that, especially for common genetic variants—the 5-HTTLPR S allele is present in about 40 percent of Caucasian populations (see above)—a “risk allele” might bear some risk of psychopathology *only* in the presence of further modulating factors, such as other genetic variations (a gene–gene interaction effect, or epistasis, or a haplotype effect, only the first one of which is covered in the present section) or environmental factors (a gene–environment interaction effect); or it might have adverse effects on one trait, but be beneficial for some other trait (a so-called pleiotropic gene effect). A molecular genetic focus on the mechanisms underlying complex human traits and disorders therefore needs to take into account these modes of behavioral modulation. In the following, evidence on such effects is sketched—again, primarily with regard to 5-HTTLPR.

5.1 Gene–gene interactions

As early as 1998, Ebstein and colleagues (Ebstein et al., 1998) observed that temperament measures in neonates were modulated by an interaction between 5-HTTLPR and a variant in the gene encoding the dopamine D4 receptor (DRD4). The latter polymorphism is a VNTR within the third exon of DRD4, where a segment of 48 bp is repeated 2 to 10 times, which potentially affects D4 receptor function (see Oak, Oldenhof, & Van Tol., 2000). The DRD4 exon III 7-repeat allele has been the focus of considerable research efforts and has been associated with higher scores in novelty-seeking (e.g. Ebstein et al., 1996; Strobel, Wehr, Michel, & Brocke., 1999). Whereas meta-analyses do not suggest a significant association between DRD4 exon III and novelty-seeking (e.g. Kluger, Siegfried, & Ebstein, 2002; Schinka, Letsch, & Crawford, 2002), the evidence on the 7-repeat allele’s role in a related phenotype, namely attention deficit/hyperactivity disorder, is rather consistent (see e.g. DiMaio, Grizenko, & Joober, 2003; Swanson et al., 2000).

In the Ebstein et al. (1998) study, the 5-HTTLPR S/S genotype was related to lower scores in orientation to novel stimuli in those neonates who did not carry the DRD4 exon III 7-repeat allele. Likewise, in a follow-up study, the scores in measures of negative emotionality were again higher in two-month-old infants who were carriers of the 5-HTTLPR S/S genotype but lacked the 7-repeat allele (Auerbach et al., 1999).

Even higher-order interactions have been reported. For the association between DRD4 exon III and novelty-seeking, it was reported that carriers of the DRD4 exon III 7-repeat allele showed higher scores in novelty-seeking especially when they also had the 5-HTTLPR L/L genotype and the Val/Val genotype of a SNP in the gene encoding the dopamine-catabolizing enzyme catechol O-methyltransferase (COMT; Benjamin et al., 2000). In a sample of our own, where we did not observe a main

effect of DRD4 exon III on novelty-seeking, we could replicate the above-mentioned pattern (Strobel, Lesch, Jatzke, Paetzold, & Brocke., 2003).

These findings indicate that, even if a genetic variant may not show replicable main effects on a given temperament trait (like in the case of the inconsistent DRD4 exon III–novelty-seeking association), its effects may become visible if other polymorphisms are taken into account (such as 5-HTTLPR and COMT Val158Met in the example provided in the previous paragraph), or the genetic variant in question may influence the mode of action of another variant (like 5-HTTLPR in the evidence sketched in the penultimate paragraph) on another, perhaps related, temperament trait (negative emotionality, which to some extent is inversely related to novelty seeking).

5.2 Gene–environment interactions

As outlined in Section 4.2, the role of the 5-HTTLPR S allele in the pathogenesis of depression is equivocal. However, as also noted, its role in modulating individual differences in neuroticism as a vulnerability factor for depression and in the function of neuronal circuits which are disturbed in depression is quite replicable. Hence the 5-HTTLPR S allele may not influence the development of depression per se, but rather impact on a vulnerability or diathesis variable, which only in interaction with stress leads to an increased risk of depression.

In a seminal study, Caspi et al. (2003) demonstrated that stressful life events such as adverse financial, medical, or psychosocial conditions were major factors impacting on the development of depressive symptoms, but that this effect was most pronounced in carriers of one or two copies of the 5-HTTLPR S. These results—which were later on substantiated by the finding that a gene–environment interaction between 5-HTTLPR and stressful life events is observed even at the level of amygdala activation by aversive stimuli (Canli et al., 2006)—could be replicated in several, (though not all) subsequent studies (for a recent meta-analysis see Risch et al., 2009); the mode of assessing or defining a stressful life event is one likely reason for inconsistencies between studies: Uher & McGuffin, 2010). Interestingly, in a review by Belsky and colleagues (Belsky et al., 2009), it was convincingly argued that the available evidence on the interaction between 5-HTTLPR and stressful life events points to higher resilience of the S allele carriers when no stressful life events are present. Hence, common genetic variants may exert their behaviorally relevant effects in an environment-contingent fashion, which explains their existence in the gene pool, as their fitness-reducing effects in one environment are outweighed by fitness enhancing effects in another environment (see also Penke, Denissen, & Miller, 2007).

5.3 Pleiotropic gene effects

In another study by Canli and colleagues (Canli et al., 2005) it was found that 5-HTTLPR not only mediates the amygdala response to aversive stimuli, but also impacts on functional and structural differences in other brain regions, including prefrontal and motor areas; this suggests a broader role for 5-HTTLPR in brain function, including cognitive and motor processes. Indeed, there is emerging

evidence that genetic variation in serotonin function impacts not only on emotional, but also on cognitive traits.

This is better illustrated using the example of another genetic variation along the serotonergic signaling pathway: the gene encoding the brain-expressed isoform of the serotonin-synthesizing enzyme, tryptophan hydroxylase 2 (TPH2), harbors a SNP in its promotor region, the TPH2 G-703T polymorphism. Although it is still a matter of debate whether this polymorphism itself affects the efficiency of gene transcription or whether it only resides near a functional variant (see Chen, Vallender, & Miller, 2008; Lin et al., 2007; Scheuch et al., 2007), the evidence on the behavioral correlates of this variant is currently quite consistent: the rare T/T genotype was associated with lower scores in measures of negative emotionality in a study by Reuter and colleagues (Reuter, Küpper, & Hennig, 2007), and a similar pattern was observed in an study of our own (Gutknecht et al., 2007). In another study, the T/T genotype was found to be associated with poorer performance in a task of executive attention (Reuter, Ott, Vaitl, & Hennig, 2007), which is in part substantiated by another finding of poorer executive control functions in T allele carriers (Strobel et al., 2007).

This evidence provides an illustrative example for a pleiotropic gene effect: a genetic variant of benefit with regard to one trait (i.e. negative emotionality) might be regarded as a vulnerability factor with regard to another trait (i.e. executive functioning) and vice versa, with the positive net effects potentially outweighing the negative ones in terms of evolutionary fitness. Hence, this example provides another explanation for the existence of common genetic variants.

6 Future Directions

This section finally sketches current directions in molecular genetic approaches to individual differences. We will briefly exemplify the potential of genome-wide association studies and epigenetic investigations (that is, studies on the role of, say, environmental factors in modulating gene expression), and will also provide a short overview of the emerging field of system genetics (that is, approaches implying systems translating genetic variation from genes to endophenotypes and behavior, for example transcriptomics, proteomics, or cellomics).

6.1 Genome-wide association studies

As already mentioned in Section 2, genome-wide association studies (GWAS) provide a fresh approach to the study of molecular genetic influences on individual differences. Using DNA microarray technologies, it is now possible to genotype individuals not with regard to their genotype of one or several candidate polymorphisms, but with regard to hundreds of thousands of variants spread throughout the genome (current GWAS use 500,000 or 1,000,000 variants located on one DNA microarray). These variants then serve as markers for gene regions, which harbor genetic variability associated with a phenotype under discussion. Thus, this approach can aid the detection of genetic variability impacting on individual differences, even if we do not know the function of the respective polymorphic genes, and thereby it can help to generate

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hypotheses on new signalling pathways potentially involved in the modulation of a given phenotype.

Of course, when applying this technique, we need to consider several issues in order to avoid false positive findings. First, if we carry out, say, 1,000,000 association tests, one for each marker on the microarray, then 5 percent, —that is, 50,000 of these tests—might be significant just by chance. Hence we must apply a correction for multiple testing—e.g. the Bonferroni correction, which in the present example would require an effect being significant at an uncorrected level of $\alpha = 0.00000005$. Second, we need very large samples to detect effects at this stringent level of significance; and, third, we need one or more large replication samples to make sure that effects detected by a GWAS are not falsely positive effects. Fourth, after GWAS and the replication of one variant (which is to be associated with a given phenotype), ideally we should move on and detail the genetic variant(s) and signalling pathways responsible for the observed association.

With regard to negative emotionality there are so far at least three GWAS on the trait neuroticism: Shifman and colleagues (Shifman et al., 2008) observed an association of neuroticism with a variant in the gene encoding phosphodiesterase-4D (PDE4D, an enzyme involved in second-messenger signalling, which presumably has a role in modulating the effects of antidepressants (Zhang et al., 2002). Although the effect could not be replicated in internal replication samples of Shifman and colleagues, the role of PDE4D in modulating negative emotionality was later substantiated by an independent group (Heck et al., 2008).

Unfortunately, in two further GWAS (van den Oord et al., 2008; Terracciano et al., 2010), PDE4D was not detected as one major factor influencing neuroticism. Rather, in these two studies, neuroticism was associated with variation in the gene encoding MAM domain containing glycosylphosphatidylinositol anchor 2 (MAMDC1), which is involved in cell adhesion, and synaptosomal-associated protein 25 (SNAP25), which modulates vesicle–membrane fusion, respectively. Although these genes may point to interesting mechanisms underlying neuroticism, we need to await further studies and meta-analyses before we can rely on consistent evidence concerning promising signalling pathways involved in the modulation of negative emotionality, and hence in vulnerability to affective and anxiety disorders. Nevertheless, the GWAS approach has a high potential for hypothesis generation and likely will dominate the field over the next years—but certainly together with the approach outlined in the next section.

6.2 Epigenetic studies

The term *epigenetics* refers to changes in gene expression which are not due to variation of the DNA itself (i.e. genetic polymorphisms). Rather, remodelling of chromatin—a complex of DNA, wrapped around proteins called histones, and of non-histone proteins—can alter gene expression, as chromatin exists in an activated state (euchromatin), which allows gene transcription, and in an inactivated state (heterochromatin), which does not allow gene transcription. The latter repression of gene transcription can be due to methylation of histones or to the DNA, which inhibits the binding of transcription factors (for an informative overview, see Tsankova,

Renthal, Kumar, & Nestler, 2007). It is important to note that such epigenetic modulation of gene transcription can be due to experiential/environmental factors in a region-/cell-specific way (i.e. DNA methylation in a cell cluster in the brain due to certain external factors will usually not be detectable if we examine the DNA methylation in blood cells).

An impressive demonstration of the crucial role of epigenetic mechanisms in the modulation of psychologically relevant phenomena can be found in a study by Weaver and colleagues (Weaver et al., 2004). They demonstrated that rats, which were raised under good rearing conditions (i.e. by “good mothers”), showed less methylation in the promotor region of the rat glucocorticoid receptor (GR) gene, and consequently, a higher GR expression than rats raised by “bad mothers.” Importantly, a laboratory stress measure showed that the latter rats showed an exaggerated stress response (in terms of corticosterone levels) as compared to the former. Importantly, this effect was not observed in rats *born* by “bad mothers,” but only in rats *reared* by “bad mothers.”

Interestingly, comparable evidence could also be obtained in an examination of human post mortem brains (McGowan et al., 2009): it was shown that, in suicide victims who had experienced childhood abuse, hippocampal GR promotor methylation was higher and GR gene expression was lower than in control subjects or suicide victims without childhood abuse. Furthermore, it could be shown that behaviorally relevant epigenetic mechanisms can be studied even using peripheral tissue extracted from blood. Philibert and colleagues recently showed that childhood abuse is associated with higher methylation in the 5-HTT gene promotor (Beach, Brody, Todorov, Gunter, & Philibert, in press), with the 5-HTTLPR S allele possibly also impacting on higher methylation of the 5-HTT gene promotor (Philibert et al., 2007). Hence this evidence extends the findings of Weaver and colleagues, by showing a comparable effect of early adverse environmental factors on epigenetic mechanisms underlying stress responses and, putatively, negative emotionality. Moreover, the latter studies demonstrate that, until methods are available to examine epigenetic regulation in specific brain regions and cell assemblies of living humans, advances in the understanding of epigenetic mechanisms can already be made by using peripheral tissue.

6.3 Beyond genomics: system genetics

The more we learn about the role of genetic variation (including epigenetic remodeling) in the modulation of individual differences, the more it becomes obvious that we need to shift our focus from the one or a handful of genetic variations to a systems view. Such levels include genetic/genomic networks (with gene–gene–interactions as an example) impacting, over molecular and cellular networks, on tissue networks such as brain networks like the BIS described above, and ultimately on organismic networks comprising brain–periphery interactions. Thus, beyond genomics, the areas of transcriptomics, proteomics, and cellomics await exploration—which, however, requires sophisticated methods. In an interesting review, Sieberts and Schadt (2007) summarize such methods for a comprehensive integration of gene variation, gene expression/co-expression, and phenotypic data to understand the complex relationships among gene expression and individual differences at the trait level. These

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network approaches will soon add significantly to the knowledge gathered by genetic association studies.

The molecular genetics approach continues to generate new evidence on the neurobiology of individual differences, and at a fast pace. The evidence summarized in this chapter can be viewed only as an example designed to provide a first insight into the field. We nevertheless hope that we were able to generate (or further) the interest of our readers in this exciting area of research.

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