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Genetics in experimental psychopathology: From laboratory models to therapygenetics. Where do we go from here?

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Abstract

Experimental psychopathology is the application of experimental methods to the study of psychopathology and its underlying processes. The study of individual differences in the development, maintenance and/or relapse of psychopathology is currently at the forefront of research. Stressful events are known to exert a substantial impact on our lives. Why however, do some people react in an extremely adaptive way, while others develop pathology in the aftermath of a trauma? One particularly interesting individual differences factor is genetic makeup and the aim of this paper is to review the current state of the art of genetics in experimental psychopathology which is illustrated by using fear conditioning as an exemplary model in the study of mechanisms underlying anxiety. We identify and discuss current challenges of the field and provide recommendations on how these can be met. In addition, criteria for experimental models of psychopathology as well as future directions are discussed.

Keywords: genetics, experimental psychopathology, fear conditioning, polymorphism, polygenic scores, recommendations

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Table of Contents

Introduction

Stressful events can have a substantial impact on our lives. Why however, do some people react in an extremely adaptive way to such (traumatic) life events, while others develop pathology in the aftermath of a trauma? There is currently no satisfactory explanation for how initial symptoms of psychopathology develop into a chronic course in some individuals but not in others, and what differentiates patients who relapse from those who do not. Moreover, even though current treatment guidelines for psychopathology contain treatments that are effective in a subset of patients, a substantial number of patients fails to respond even after trying several treatments sequentially (Ravindran & Stein, 2010).

A whole array of individual difference factors may play a decisive role in the development, maintenance and/or relapse of psychopathology such as sex/gender or personality traits. One particularly interesting individual differences factor is genetic makeup. In recent years, knowledge on genetic markers and the availability of relatively cheap DNA analysis methods have sparked the fields of behavioral and psychiatric genetics. After initial great optimism that the mapping of the human genome (http://www.genome.gov/10001772) would bring genetic markers for psychopathology within reach, researchers have struggled with the fact that single genes exert only small effects, especially with regard to complex psychiatric diagnoses, combined with the heterogeneity of disorders as currently classified in the DSM (American Psychiatric Association, 2013) and the ICD (Dilling, Mombour, & Schmidt, 2013). Hence, in trying to understand psychopathology and its underlying biological (i.e. genetic) underpinnings, bridges need to be built to span the enormous gap between genetic variations that exert effects at a molecular level on the one hand, and psychiatric diagnoses and behavioral traits on the other. This is exactly where experimental models of psychopathology come in. The field of experimental psychopathology is defined as the application of experimental methods to the study of psychopathology and its underlying processes. Hence, this field aims at understanding pathological processes by breaking down complex constructs and behaviors into isolated mechanisms that may be studied independently of the pathology itself. Models from the field of experimental pathology may therefore serve as intermediate constructs, or endophenotypes (see box for glossary), to elucidate how genetic variation underlies normal variation of behavior.

As will be reviewed in the following sections, endophenotypes derived from highly controlled laboratory experimental psychopathology experiments have been (successfully) associated with genetic factors, thereby aiding the translation between genetic factors on the one hand and the (propensity for) development of psychiatric disorders on the other hand. The aim of this paper is to review the current state of the art of genetics in experimental psychopathology by

using fear conditioning as an exemplary model, without aiming to provide a comprehensive review of findings in the field. We identify and discuss current challenges of the field and provide recommendations on how these can be met. In addition, criteria for experimental models of psychopathology as well as future directions are discussed that need to be fulfilled for valid application of the candidate gene approach and its extensions (e.g. polygenic scores).

The Candidate gene approach

Promises.

Candidate gene studies have been at the forefront of genetic association studies in psychology and psychiatry. These studies focus on the selection of genes that are *a-priori* implicated in the etiology of the disease/trait to be studied. This link may be based on biological plausibility of the gene's function and its relevance in the mechanism of the disease or trait (Kwon & Goate, 2000; Patnala, Clements, & Batra, 2013). Once a target gene is identified, common variations ('polymorphisms', see glossary) in this gene are targeted that (optimally) have a known functional consequence such as affecting gene regulation or the protein product (Kwon & Goate, 2000). Finally, the genetic polymorphism is investigated with respect to an association (i.e. statistical correlation) with the disease/trait.

A prime example in the field of genetics in experimental psychopathology is the gene that codes for the serotonin transporter (*5-HTT*), the target protein for the first-choice pharmacological treatment of depression and anxiety (i.e., the selective serotonin reuptake inhibitor, SSRI). It has long been known that serotonin plays a role in the pathogenesis of anxiety in rodents and humans (Baldwin & Rudge, 1995). Consequently, there is biological plausibility and solid *a-priori* evidence for a possible link between anxiety and depression, genetic variance in the serotonin system in general, and this gene in particular. Within the *5-HTT* gene promoter, a common polymorphism referred to as the serotonin-transporter linked polymorphic region (*5-HTT*LPR) has been identified that affects the in vivo availability of 5-HTT protein in the presynaptic membrane (Heils et al., 1995; Lesch et al., 1996). Together with the a-priori biological plausibility linking variation in the neurotransmitter system with the disease, the evidence for functional impact of this polymorphism on the serotonin transporter provides a solid justification of gene and gene variant selection (i.e. candidate gene). Initial reports generated excitement about the association of the *5-HTT*LPR with anxiety-related traits (Lesch et al., 1996) and susceptibility to depression in interaction with life events (Caspi et al., 2003). A few prominent examples of subsequent meta-analyses that have established reliable associations with the *5-HTT*LPR include anxiety-related personality traits (Munafò et al., 2009; Sen, Burmeister, & Ghosh, 2004), amygdala reactivity (Munafò, Brown, & Hariri, 2008), emotional attention biases (Pergamin-Hight, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2012) and antidepressant efficacy (Porcelli, Fabbri, & Serretti, 2012). Nevertheless, not all observed effects have been proven reliable, and developmental processes have been found to underlie some effects (Kobiella et al., 2011), which have led to alternative conceptualizations related to gene x environment (see 4.; e.g. Homberg & Lesch, 2011) and epigenetic processes (e.g. de Geus & Middeldorp, 2013).

Pitfalls and recommendations.

Following the exciting first wave of publications using the candidate gene approach in the first decade of the 21st century, such studies have recently tended to fall out of favor due to several reasons (Dick et al., 2015; Duncan & Keller, 2011; Tabor, Risch, & Myers, 2002). In particular, this is due to non-replications of previously reported exciting new findings (Ioannidis, Ntzani, Trikalinos, & Contopoulos-Ioannidis, 2001), the lack of valid replication studies, and the realization that the phenomena that were being studied were likely to be affected by not one single variant, but by many different loci, each with a small effect (as in e.g., personality traits: Munafò & Flint, 2011). In addition, the ease of using *post-hoc* testing of multiple associations in combination with reporting biases in favor of significant findings in largely underpowered studies (Hewitt, 2012; Johnston, Lahey, & Matthys, 2013) has nourished skepticism.

It is clear that the field of genetics in psychology and psychiatry would profit enormously from the existence of guidelines to adhere to and to realign as a research field in order to balance the reduction of false positive reports against the reduction of the number of interesting novel findings. This has led to initiatives such as guidelines for how to report genetic association findings (STRTEGA, Little et al., 2009), and the recent launch of editorial policies to achieve a certain quality control for candidate gene studies at several (psychological and psychiatric) journals such

as *Behavioral Genetics* (Hewitt, 2012) or the *Journal of Abnormal Child Psychology* (Johnston et al., 2013), *Psychological Science* (the journal refers to Hewitt, 2012) and *Biological Psychiatry* (http://www.elsevier.com/journals/biological-psychiatry/0006-3223/guide-for-authors). These guidelines and editorial policies highlight criteria that need to be fulfilled for basic validity of the research, and journals apply them for consideration of a manuscript as well as its evaluation. They include for instance basic design criteria with regards to adequate (i.e. large) sample size, definition and assessment of the phenotype, statistical corrections and population stratification (see glossary). In addition, specific criteria are formulated with regards to biological plausibility and gene and polymorphism selection (all guidelines are compiled in BOX 2). As such, these recommendations do not only serve for the purpose of editorial decision making, but can also be regarded as guidelines for the research field of genetics in experimental psychopathology. If these prerequisites are met, the candidate gene approach can be a valid means for generating highly valuable and reliable insights. One such prerequisite represents the careful section of the phenotype, which we will discuss in the following.

Definition of psychiatric (endo)phenotypes

Current definitions of psychiatric phenotypes.

In addition to the selection of one or more genetic candidates, the accurate and appropriate definition of a heritable phenotype is critical to the success of molecular genetic (association) studies (Cross-Disorder Phenotype Group of the Psychiatric GWAS Consortium et al., 2009). It has been shown that when it comes to conceptual replication, failure to replicate can originate from varying definitions of the phenotype (Noble, 1998). Traditionally, phenotypes in psychiatric genetics research are defined as clinical diagnoses based on classification systems like DSM-5 and ICD-10 (DSM-5: American Psychiatric Association, 2013; ICD-10: Dilling et al., 2013) and the same applies to experimental psychopathology. Even though categorization into distinct disorders is useful from a clinical point of view and has led to major advances in epidemiological studies, the categorical nosology based on DSM-5 and ICD-10 has severe draw-backs when it comes to clinical genetic (association) studies. During the past decade, major advances in understanding the neurobiological and genetic underpinnings of anxiety disorders that are derived in part form experimental psychopathological research have repeatedly shown that the binary classification of psychiatric disorders by the traditional diagnostic systems does not align with advances of neurobiological research (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; The Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium, 2015).

Advances in neurobiology may inform novel definitions of phenotypes.

Molecular genetic studies as well as quantitative genetics have suggested already decades ago that the genetic influence on anxiety disorders transcends the boundaries of diagnostic categories (Smoller & Tsuang, 1998). Recently, there is accumulating evidence from genome-wide association studies (GWAS) that several psychiatric disorders in fact share genetic risk factors (e.g., panic disorder and bipolar disorder, anxiety disorders and major depression; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Doherty & Owen, 2014). This is also reflected in the high degree of comorbidity between diagnoses (Cross-Disorder Phenotype Group of the Psychiatric GWAS Consortium et al., 2009). Furthermore, DSM-5 and its ancestors have explicitly aimed at being a-theoretical and descriptive and have not yet been able to base their diagnostic categories on neurobiological evidence. Consequently, what has proven useful from a clinical point of view may not be optimally suited for clinical genetic studies as psychiatric diagnoses do not seem to correspond to distinct genetic entities (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Doherty & Owen, 2014). Pre-clinical experimental research on psychopathology has contributed greatly to this challenge, which represents a prime example of how completely different disciplines (psychiatric nosology and neuroscience or molecular genetics) can cross-foster each other.

One approach to minimize the arbitrary nature of categorical diagnoses and the resulting loss of information is to consider traits relevant to psychopathology on a continuum from adaptive to maladaptive functions (e.g. Insel et al., 2010a; Insel, 2014). This could concern observable traits (phenotype), such as avoidance behavior, or parameters that may not be directly observed such as physiological reactivity (e.g., in the startle reflex) (Insel, 2014), which requires specific tools for its measurement. This dimensional approach fits well in the experimental psychopathology

tradition, and allows for variance (rather than a dichotomization in presence vs. absence of a symptom/diagnosis) in the phenotype and considers clinical heterogeneity that is not captured by the diagnosis itself. In a first attempt to overcome these problems posed by categorical classification of disease, a focus on sub-traits and specific symptoms associated with a complex clinical phenotype or diagnosis has been suggested as one promising approach for the identification of specific biomarkers or endophenotypes (Gottesman & Gould, 2003). The rationale behind this is that heritability of these endophenotypes that cut across cross-heritable and comorbid disorders is likely to be genetically less complex structured. Hence, genetic associations with such endophenotypes should be more easily detectable. Such a dimensional view may also more accurately capture the complex underlying genetic architecture with the different symptoms within a syndrome/clinical diagnosis possibly being under the control of distinct genetic loci (and environmental factors), yielding varying degrees of severity.

To foster the development towards new avenues for the classification and treatment of psychiatric disorders, the National Institute of Mental Health (NIMH) has initiated the Research Domain Criteria (RDoC) project (http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml). This project strives for the definition of pathology based on malfunctions within distinct neural circuits in order to overcome the lack of trans-dimensionality of the traditional diagnostic systems. Indeed, to advance the search for endophenotypes in psychiatry that allows the study of the genetic architecture of disease, models from experimental psychopathology are needed to bring the field forward.

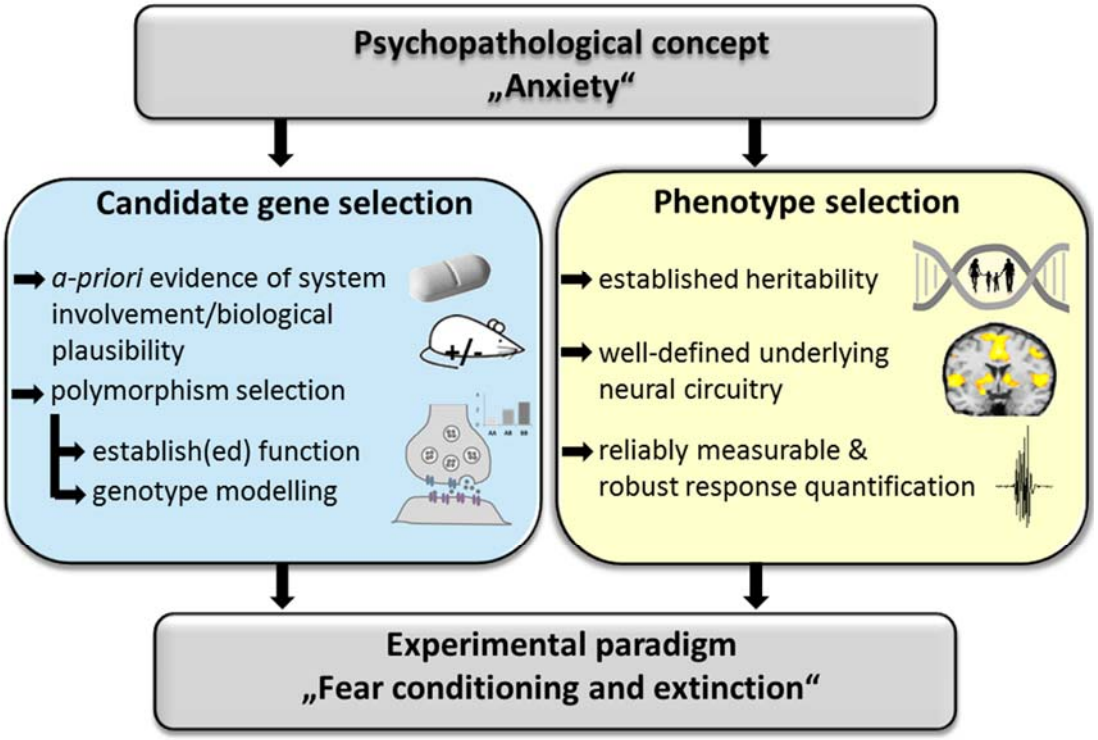

Figure 1: Schematic outline of recommended criteria for the evaluation of the appropriateness of a behavioral paradigm for genetic association studies.

Up to now, the endophenotype approach has generally not yielded stronger associations or larger genetic effects than approaches using the complex clinical phenotypes (Flint & Munafò, 2007). This lack of success up to date probably reflects the complex etiology of psychiatric disorders involving genes but also environments, but may also be due to not having determined the right parameters to serve as phenotype. In the future, the success of psychiatric, experimental psychopathological and behavioral genetics will critically depend on the definition of appropriate and heritable phenotypes that correspond to genetic entities (see Figure 1). This may in fact represent the “rate-limiting step” for the success of psychiatric genetics research (cf. Smoller & Tsuang, 1998). In an attempt to address the challenge of appropriate definition of the phenotype, the NHMH has launched the Phenotypes and eXposures

(PhenX) initiative (https://www.phenx.org) to reach consensus on what outcome measures and measures of environmental factors that may impact genetic effects should be recommended for future studies.

Fear conditioning as an exemplary model for genetics in experimental psychopathology

From the many successful experimental models of psychopathology, fear conditioning is one of the prototypical paradigms for the experimental study of anxiety. It has been the predominant model for the etiology of anxiety disorders (Lissek et al., 2005; Duits et al., 2015) and parameters derived from this model represent promising endophenotypes for experimental anxiety research. In this section, we will use fear conditioning as an example to illustrate the role of genetics in experimental psychopathology. We will first outline the experimental paradigm, provide details on the feasibility for genetic studies and give a brief outline of the current state of research.

Fear conditioning, extinction and return of fear as laboratory models for the acquisition, treatment and the relapse of fear.

In general, fear conditioning has been established as an outstanding, valid and widely used translational model to investigate (clinical) anxiety (Milad & Quirk, 2012; Vervliet & Raes, 2013): (1) it recreates etiological conditions believed to underlie most anxiety disorders, (2) it can be applied similarly across many different groups including healthy humans and anxiety patients, (3) it allows direct translation of knowledge on neurocircuitry and neurochemistry of fear processes from laboratory animals to humans and (4) it is a time and cost effective way to create fears in the lab under high experimental control.

Accordingly, fear conditioning plays a major role in psychological theories of anxiety disorders such as phobias (Seligman, 1971) panic disorder (Bouton, Mineka, & Barlow, 2001) and posttraumatic stress disorder (Orr et al., 2000). During fear conditioning, the organism is confronted with a neutral stimulus (e.g., a picture), which predicts an aversive event (e.g., an electric shock). Under these circumstances, the picture presentation alone will be sufficient to elicit the typical fear reaction. The shock represents the threatening event, and is commonly termed the unconditioned stimulus (US). The picture represents stimuli that co-occur with the threat, and is termed the conditioned stimulus (CS). In cognitive terms, the organism learns that the CS is a reliable predictor of the dangerous US, evokes anticipatory (fear) reactions accordingly and mobilizes defensive reaction mechanisms. Yet, some individuals display maladaptive learning mechanisms eventually leading to pathology as can be seen in the development and maintenance of anxiety disorders.

Extinction (i.e., the waning of fear as a result of the CS being presented in the absence of the US) has obvious implications for the treatment of phobias and other anxiety disorders (Anderson & Insel, 2006). Indeed, it inspired the exposure therapies that have provided highly effective treatments of anxiety disorders (Barlow, 2002). Cognitive behavioral therapy (CBT) represents a learning process leading to symptom relief and long-term changes in behavior that have measurable correlates in neural activation patterns, synaptic connectivity and gene expression patterns (Linden, 2006).

Even though extinction-based treatment of anxiety disorders is effective, fear tends to return (relapse). There is considerable individual variation in the susceptibility to return of fear or relapse in clinical terms (Goode & Maren, 2014, Haaker et al. 2014) and strategies for relapse prevention based on experimental work in healthy humans (Vervliet, Craske, & Hermans, 2013) might profit from targeting specifically susceptible groups.

Consequently, fear conditioning, extinction and return of fear manipulations serve as valid laboratory models for the acquisition, treatment and return of pathological fears. Understanding the molecular pathways that mediate experimental conditioning and extinction might therefore make an important contribution to the study of anxiety pathophysiology, resilience and treatment mechanisms

A prototypical model for the study of genetics in psychopathology.

Fear conditioning and extinction represent particularly promising models for genetic studies for several reasons (see Figure 1). First, both human (Hettema, Annas, Neale, Kendler, & Fredrikson, 2003) and animal studies (Royce, 1972) have shown that genetic factors represent a significant source of individual variation in the habituation, acquisition, and extinction of fear. Specifically, about one third of the variance in both human fear conditioning (Hettema et al., 2003) and the risk to develop anxiety disorders (Gordon & Hen, 2004) can be attributed to genetic factors. Established heritability of the behavior/trait to be studied is of course a major prerequisite for even considering studying its specific genetic underpinnings. Second, the same applies to within-subject reproducibility of the behavior at test and test-retest reliability which has been established for fear conditioning and return of fear despite of the learning element inherent in these paradigms for both SCRs (Zeidan et al., 2012), and FPS (Torrents-Rodas et al., 2014).

Third, the neural network underlying fear conditioning and extinction has been studied intensively in both animals and humans (Fanselow & LeDoux, 1999; Herry et al., 2010; LeDoux, 2000; Milad & Rauch, 2007; Sotres-Bayon & Quirk, 2010). A well delineated neural network allows close inferences between the activity of a limited neural circuitry and the behavioral outcome, all but guaranteeing close correspondence between genetic effects at the molecular level and the (endo)phenotype. It has been argued for imaging genetics that phenotypes from neuroimaging are more closely related to the neurobiological level at which the genetic variation exerts its effects. This close relation suggest a tighter coupling between variation at the molecular level and the endophenotype, yielding much stronger 'penetrance' of genetic variation on the neurobiological level than on behavior (Meyer-Lindenberg, 2012). Likewise, (endo)phenotypes derived from basic behaviors that are known to originate from a very well-described neural circuitry have higher penetrance than complex behavioral or psychological (trait) factors. With respect to the different read-out measures that have been used to assess fear responding in conditioning paradigms, different levels of penetrance may also be assumed. For example, the behavior may be assessed with a physiological outcome measure such as fear-potentiated startle (FPS), which originates directly from activity in amygdala-centered defense systems (Davis, 1989). In contrast, subjective reports are subject to cognitive evaluations and experimenter demand and are hence, arguably, associated with a more complex neural network. In fact, genetic association studies in fear conditioning and extinction have found reliable associations with FPS but not with measures that are more dependent on cognitive evaluations such as skin conductance responses (SCRs) and subjective ratings (Heitland et al., 2012; Klucken et al., 2012; Klumpers, Heitland, Oosting, Kenemans, & Baas, 2012; Lonsdorf, Weike et al., 2009, 2010) . As subjective ratings depend on a more complex neurocircuitry, they arguably have a lower rate of neurobiological penetrance than FPS.

Fourth, fear responses can be easily and reliably measured using physiological measures such as FPS and/or SCR and importantly, twin studies have proven the plausibility of such measures (Hettema et al., 2003; Merrill, Steinmetz, Viken, & Rose, 1999) for the study of the heritability of conditionability. Furthermore, insight from animal research can be translated in a straightforward manner to human research because similar measurements (most notably FPS) can be used in both animal and human.

During the past six years, we have seen an increasing number of publications in the field of genetics in experimental fear conditioning and extinction studies as well as in therapygenetics (i.e. using genetic markers to predict response to psychological treatment (Lester & Eley, 2013; Lonsdorf, Rück et al., 2010)) studies and other attempts to translate experimental findings to the clinics. This field of research has been reviewed before (Lonsdorf & Kalisch, 2011) and an in-depth review of the reported genetic associations is beyond the scope of this paper. We therefore limit ourselves to some prime examples that are based on strong *a-priori* biological plausibility, an important criterion for a valid candidate gene approach (see Figure 1).

For instance, pharmacological evidence implicates both the serotonin (5-HT) and corticotrophin-releasing hormone (CRH) systems in the acquisition and expression of fear. The previously discussed polymorphism in the *5-HTT* gene (*5-HTT*LPR; introduced in section 2.1) has been successfully associated with fear conditioning by means of classical conditioning (Lonsdorf et al., 2009; Wendt, 2014), instruction (Klumpers et al., 2012) and observational learning (Crisan et al., 2009).

The *5-HTT*LPR is a prime example of a polymorphism of which the functional consequences have been studied (see references in section 2.1). However, molecular evidence on the functional effects of a given polymorphism or the

expression level associated with different variants is not always available. This is the case for polymorphisms in the corticotropin-releasing hormone (CRH) neurotransmitter system. CRF plays an important role in stress responses (Lowry & Moore, 2006), not only through its action in the hypothalamic–pituitary–adrenal (HPA)-axis, but also as a neurotransmitter in regions outside of the hypothalamus relevant for fear responding (e.g., amygdala, hippocampus, medial prefrontal cortex) (Hauger, Risbrough, Brauns, & Dautzenberg, 2006). Preclinical studies have indicated involvement of the CRH system in the acquisition of cue and context conditioned fear (Bijlsma, van Leeuwen, Westphal, Olivier, & Groenink, 2011; Risbrough et al., 2009; Roozendaal, Schelling, & McGaugh, 2008). However, these findings have been difficult to translate to the human domain because of the lack of pharmacologic agents that are safe to use in humans. In this case, studying a polymorphism in the gene coding for the centrally expressed CRH 1 receptor that has been associated with panic disorder (Keck et al., 2008) allowed for a first tentative translation of these preclinical findings to the acquisition of FPS to a conditioned cue (Heitland, Groenink, Bijlsma, Oosting, & Bass, 2013; replicated in a follow-up study, Heitland & Baas, in prep).

Other neurotransmitter systems have been the focus of analysis when it comes to fear extinction. Pioneering such analyses, a functional single nucleotide polymorphism (SNP) in the gene coding of the enzyme *COMT* (*COMT*val158met) that degrades dopamine was studied because of a-priori evidence for a role in behavioral flexibility vs. stability (Bilder, Volavka, Lachman, & Grace, 2004), a process that arguably affects fear extinction. Indeed, genetic variation in *COMT*val158met was significantly associated with delayed fear extinction in the laboratory (Lonsdorf et al., 2009; but see: Raczka et al., 2011 for immediate extinction). Moreover, this polymorphism is associated with deficient fear inhibition (Wendt, 2014) as well as outcome of exposure-based treatment (Lonsdorf, Rück et al., 2010). Another system that has received attention in relation to extinction is the cannabinoid system, after preclinical findings that this system is crucial for extinction of fear (Marsicano et al., 2002). As with the CRH system, the lack of specific pharmacologic agents to translate this preclinical insight meant that the translation to humans was lagging behind. A genetic analysis of polymorphisms in the gene encoding for the centrally expressed cannabinoid 1 receptor (CNR1) was shown to affect the extinction of conditioned fear in humans (Heitland et al., 2012).

Another prominent example is a functional SNP in the pro-domain of the gene coding for brain derived neurotrophic factor (*BDNF*val66met). There is a rich preclinical literature on BDNF effects and hippocampus- as well as amygdala dependent learning (Ou & Gean, 2006; Rattiner, Davis, & Ressler, 2004, 2005; Tyler, Alonso, Bramham, & Pozzo-Miller, 2002). As such, it has been implicated in both the acquisition as well as the extinction of fear. In humans, the *BDNF*val66met polymorphisms has been linked to fear acquisition and its retention (Lonsdorf, Weike et al., 2010; Lonsdorf et al., 2014), fear generalization (Mühlberger et al., 2013) but also to extinction in rodents and humans (Soliman et al., 2010 even though the latter is debated [see Lonsdorf & Kalisch, 2011]) as well as response to CBT (Felmingham, Dobson-Stone, Schofield, Quirk, & Bryant, 2013; Fullana et al., 2012).

Despite of publications on new a-priori candidate gene studies, new developments in the field of genetics of fear conditioning include the recent emergence of functional brain imaging studies (Klucken et al., 2012; Klucken, Kruse, et al., 2014; Klucken, Schweckendiek, et al., 2014; Lonsdorf et al., 2014), the investigation of appetitive conditioning (Klucken, Kruse, et al., 2014), the incorporation of stressful life-events (Hermann et al., 2012) and contextual fear conditioning (Baas & Heitland, 2014; Heitland et al., 2012; Heitland et al., 2013; Nees et al., 2011) as well as fear generalization (Mühlberger et al., 2013). In addition “large data” or mega-analysis initiatives originating from collaborative research centers are emerging that present converging data for a certain polymorphic variant at a multidimensional and multimethodological level including conceptual replications (Reif, 2014; Straube et al., 2014).

Gene x environment interaction

So far we have discussed genetic variants as individual differences factors in experimental psychopathology. Whether behavior is affected by nature (genes) or by nurture (environment) has been discussed for centuries. Now, there is wide acceptance that behavior is affected by both environmental and genetic factors as well as their interplay (gene x environment interaction, GxE). Landmark candidate gene studies targeting GxE effects findings on the *5-HTT*LPR by Caspi et al. (2003) drew attention to the potential power of analyzing genetic factors in relation to environmental factors such as previously encountered traumas and stressors. This was followed by a wealth of studies targeting GxE interactions and focusing on the *5-HTT*LPR in humans as well as rodents (Bartolomucci et al.,

2010; Carola et al., 2008; Jansen et al., 2010; Lewejohann et al., 2010). As many genes exert their effects most strongly during development, early life stressors have been suggested as major factors shaping the neural system, sometimes in an adaptive way (Belsky & Pluess, 2009; Schmidt, 2011).

Genetics research in experimental psychopathology has so far not caught up on this trend, and a comprehensive review of this interesting research field is beyond the scope of this paper. Yet, it must be noted that the literature on GxE interaction challenges some (previously) widely accepted concepts in the field of psychiatric/psychological genetics. In light of this, the consideration of a certain allele as a "risk allele", being associated with risk for the development of a certain pathology, represents an overly simplistic view. In fact, it is not likely that a certain variant is maintained throughout evolution when only negative effects are transmitted. One conceptualization has been that of 'differential susceptibility', with certain genetic backgrounds promoting increased risk for pathology in adverse environments, but increased gain of function in nurturing environments (Belsky et al., 2009). For the *5-HTT*LPR s-allele, increased negative affectivity may be the negative side of the coin, while superior performance in several cognitive tasks have prompted the suggestion that this hypervigilance also promotes advantages in some environments where threats and opportunities may be predicted, but disadvantages in other environments (Homberg & Lesch, 2011). Unfortunately, as with candidate gene studies, candidate gene x environment studies have also suffered from a low replication rate, likely resulting from publication bias and many studies being underpowered (Duncan & Keller, 2011). New developments moving beyond candidate gene studies (see next section) will also help this field forward.

With respect to the underlying biology, GxE studies are inherently linked to a relatively new field of epigenetics which arises rapidly as a promising research area for (experimental) psychopathological research (Bagot & Meaney, 2010). Epigenetics targets a network of chemical tags that control gene expression in an experience-dependent manner such as DNA methylation and histone modifications (Goldberg, Allis, & Bernstein, 2007). Consequently, GxE interactions can be expected to be related to epigenetic modifications (Liu, Li, & Tollefsbol, 2008). However, there are some obstacles in this research field that are difficult to conquer, such as drawing inferences about epigenetic profiles in neurons from peripheral cells (Albert, 2012) because epigenetic tags are per definition cell-type and region specific and brain tissue from living humans is not accessible. The future will thus show to what extend individual differences in humans can be explained by epigenetic modifications and how appropriate epigenetic markers are as diagnostic or prognostic biomarkers.

Beyond single gene association studies

Generalization of the candidate gene approach: polygenic scores.

One critique to candidate gene approaches is that they are inherently reductionistic while research has shown that heritability for complex traits and disorders is largely due to many DNA variants each with a small effect size. Consequently, it is unlikely that one genetic polymorphism in a single gene provides a simple answer to the complex question of how behavioral traits come about. For instance, let's assume based on the literature, that the serotonin system is involved in modulating fear responses (Bauer, 2015). Now, having established biological plausibility, we may identify the functional *5-HTT*LPR as a promising candidate. This polymorphism however represents only one functional acting point in one of many critical bottlenecks within the serotonin system and functional consequences of variants are not (yet) always crystal clear. Thus, our study would be inherently reductionistic and simplistic. Hence, just like traditional clinical diagnoses based on DSM and ICD, traditional single-polymorphism candidate gene studies dichotomize individuals and neglect the dimensional spectrum of variance that is inherent both in the functionality of a biological system as well as in individual differences.

To account for this biological and phenotypic complexity, it seems self-evident to combine multiple individual genetic variants into one common score. This would more accurately capture possible variation within one system, at the cost of resolution at the molecular level (i.e., it is not possible to formulate a simplistic model of more or less functionality of one particular receptor or transporter protein that accounts for the phenotype). During the past decade, several authors and consortia have suggested the use of aggregated polygenic scores even though labelling of this approach varied (polygenic susceptibility scores, genomic profile, SNP sets, aggregate risk score (Plomin, 2013;

Plomin & Simpson, 2013). Here, the term aggregate polygenic score is adopted, as it avoids implicit assumptions with respect to risk and resilience, that might differ dependent on the outcome variable (Belsky et al., 2009). Such *aggregate polygenic scores* can either be based on the mere evidence of an association with a trait indicative of relative risk or resilience, such as the polygenic analysis of body weight which has showed increasing body weight with increasing number of previously reported "risk" genotypes (Belsky et al., 2012; Speliotes et al., 2010), or by departing from the association of a transmitter system with a certain trait, that is a set of genes that interact biologically (Nikolova, Ferrell, Manuck, & Hariri, 2011; Stice, Yokum, Burger, Epstein, & Smolen, 2012).

Both polygenic approaches, whether based on previous evidence and based on biological functionality (see above), require the assignment of a specific score to each allele of a certain polymorphism. This assignment is obviously more straight-forward in case of *a-priori* evidence of an association with a trait, as where the (risk) scores can simply be summed up (Plomin & Simpson, 2013) (but see the discussion on the concept of risk allele in the previous section). In case of score assignment based on (assumed) biological functionality, there is more "researchers-degree-of-freedom" and this "pathway-based" approach represents a broadening and generalization of the candidate-gene approach. Even though there are only few such examples published, it is evident, that different authors did not always assign the same functionality score to the same genotype, for instance with regard to the met/met genotype of the *COMT*val158met polymorphism which affects dopamine degradation (Nikolova et al., 2011; Stice et al., 2012). In addition, it is difficult to assign a positive or negative functionality score to polymorphisms located in and affecting receptors that may function both as post- as well as autoreceptors (e.g. 5-HT1a). Furthermore, the mere integration of many polymorphisms within many genes into a single index gives equal weight to all alleles, while some variants exert a more prominent influence than others, raising the necessity for weighted scores. Additional issues that would need to be accounted for are he (albeit unpredictable) effects of allele dominance and epistasis.

It is evident that these approaches are still in their infancy and that there are no straightforward recommendations with respect to the aforementioned issues, but they represent a step in the right direction of living up to the biological complexity of complex diseases or behavioral traits. As such, polygenic scores imply dimensionality of both biology and traits and acknowledge that common disorders and resilience in fact might represent extreme poles of dimensional, normally distributed traits. Consequently, the suggestion of polygenic scores fits well in the field of experimental psychopathology and hits the zeitgeist as it fits well into the NIMH launched RDoC initiative (see discussion above (Insel et al., 2010a)), which is based on similar assumptions with respect to psychiatric nosology, and publications adopting a polygenic approach are recently now increasing (Meyers et al., 2013; Pearson-Fuhrhop et al., 2014; Peyrot et al., 2014; Whalley et al., 2012), albeit not yet in the field of experimental psychopathology.

An outlook on the future

Currently, we are in the middle of a technical revolution with prices for genotyping falling rapidly and new tools becoming available. One example are DNA arrays containing genetic variants of relevance for specific disorders/traits (e.g. the CardioChip (Zimmerman et al., 2010) for cardiovascular functioning or the ImmunoChip (Cortes & Brown, 2011) for immunology). A similar array has been developed for behavioral/temperamental or psychiatric traits by the Psychiatric Genomics Consortium (http://www.med.unc.edu/pgc/psychchip), and behavioral genetics and genetics in experimental psychopathology may profit profoundly from this technological revolution. The flipside of these decreasing cost and increasing mounds of data, is the ease of *a-posteriori* hypothesis generation and publication biases, which has increased skepticism about single-gene association studies.

The issue of the ease of running many analyses post hoc and selecting the one with a favorable outcome might be addressed for instance by *a-priori* genotyping approaches (selectively invite participants depending on genotype) or pre-registration of studies as offered by certain journals (e.g. *Registered Report* at the journal Cortex). A related initiative from the American Psychological Society (APS) is the recently launched *Registered Replication Reports* (http://www.psychologicalscience.org/index.php/replication) at the journal Perspectives in Psychological Science. These represent multi-lab, high-quality (direct) replications of important psychological experiments in an attempt to incentivize replication studies. This serves not only to counteract the file drawer problem (Rosenthal, 1979) but also to appreciate the central role of replication as a cornerstone of science. Such initiatives may also part of the publication bias in the domain of behavioral genetics, as both from the author's and the journal's perspective null findings are considered difficult to interpret. Therefore, well-powered and a-priori defined studies may still not be

published when the outcome was not as hypothesized. Consequentially, this program aims at promoting publication of well-designed replication studies regardless of statistical significance of the result and the size of the effect to achieve adequate estimation of the true effect size.

Recently, several online initiatives within the field of psychology have been launched, for instance the *Psych File Drawer* which provides a repository where replications can be uploaded and viewed and the *Reproducibility Project* (Collaboration, 2012), an open, large-scale, collaborative effort to systematically examine the rate and factors that predict reproducibility in psychology. On a smaller scale, initiatives such as the commitment to share data between laboratories within networks in the field (an example is a network initiated by the authors of this paper and others, see acknowledgements) and publish null-findings together may help to counteract the file drawer problem. To date, publication of null-findings are however rare (for an exception see e.g. Torrents-Rodas et al., 2012)

In addition to technical advances in molecular genetics and bioinformatics tools, novel computational models of behavior (Saez, Set, & Hsu, 2014) might aid linking genotype data to behavioral phenotypes through mechanistic pathways. While these technical and computational advances hold great promise for unraveling the neuro-genetic underpinnings of psychopathology, these rapid developments also bear some major logistical challenges. In particular, the mounds of data need to be collected, organized and analyzed, a task that goes way beyond traditional psychological or psychiatric education as it requires not only fundamental knowledge in biology and genetics but also comprehensive programming and bioinformatics skills. Consequently, working at the intersection between multiple fields requires close collaboration between different professions such as psychologists, clinicians, neuroscientists, geneticist and bioinformatics. In addition, large sample sizes are required for these projects that can only be achieved through collaborative research efforts. Another challenge that is encountered in this research field due to its strong social relevance is communication between researchers and the public. It is important to adequately inform the public and the press about potentials, promises and pitfalls of this kind of research. In particular studies revealing genetic associations with a certain behavioral trait or psychiatric condition are often hotly debated as conclusions are greatly overstated and cautionary remarks ignored in the news. It is obviously the researchers' responsibility to appropriately nuance their findings in scientific papers. Still, one may for instance encounter a headline such as "Gene for depression found" that refers to a study showing a genetic association between a certain genotype in a polymorphisms of a gene and depressive symptoms that may explain approximately 1.5% of the variance in this respective trait. In order to put such headlines into the right perspective, the media and the public has to be educated allowing them to critically evaluate such statements.

In sum, translational work cross-linking different disciplines will be powerful in unraveling the neurobiology of psychopathological mechanisms, such as fear learning and extinction processes. A primary additional value of genetic studies is to help delineate which neurotransmitter systems are associated with mechanisms of disease, even in the absence of currently applicable pharmacological tools in humans. Advances during the next decade can be expected in particular in targeting patient populations that do not respond to or tolerate standard treatments. In particular new perspectives for pharmacological interventions targeting specific neurobiological pathways (Bontempo, Panza, & Bloch, 2012; de Quervain et al., 2011; Haaker et al., 2013; Heitland et al., 2012) or genes (Eley et al., 2012; Eley, 2014; Lester & Eley, 2013; Lonsdorf, Rück et al., 2010; Roberts et al., 2014) for enhancing CBT outcome hold big hopes for better anxiety treatments in the future. Such studies aim to identify biomarkers with high sensitivity and high diagnostic specificity that reliably predict treatment outcome.

Furthermore, advances in the neurosciences have already helped to re-define diagnostic boundaries and aided the development of new classification systems for psychiatric disorders (RDoC)(Insel et al., 2010b). Research targeting the pathways to the development of pathology, both in experimental and clinical terms, is necessary to gain deeper insight in the biological underpinnings and pathways behind these conditions which is a necessary prerequisite for the development of new (possibly individualized) treatments as well as prophylactic and early intervention programs in the future. Even though the field of genetics in experimental psychopathology is still in its infancy we anticipate major advances during the next decade. Striving towards the ultimate future aim is to foster individualized treatments for psychiatry and psychology (also dubbed 'the precision medicine revolution').

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Glossary

technical term	definition
allele	Alternative form of a gene at a specific locus
anonymous variants	Polymorphic variation with unknown effect on gene function
candidate gene	A gene who's function suggests a possible association with a trait/disease. Serotonergic genes are for instance considered candidate genes for mood and anxiety-related processes.
epigenetics	DNA methylation and histone modification processes that exert an impact on gene expression without affecting DNA sequence.
epistasis	Non-additive interaction between different genes located at different loci. The effect that the variant of one gene has on a trait is dependent on the variant of the other gene.
SNP	Single nucleotide polymorphism (SNP, pronounce 'snip')
endophenotpye	A measurable factor, which is not directly observable, that lies in the pathway between a disease (i.e., observable phenotype) and the genotype. As such, an endophenotype is not a risk factor but rather represents a manifestation of the underlying disease liability (for a discussion see Lenzenweger, 2013)
functional polymorphism	A polymorphism of which effects have been demonstrated on the neurochemical level
gene expression	Transcription of DNA to mRNA
genotype	The combination of different alleles at the same gene locus
heritability	The amount of variance in the phenotype that can be attribute to genetic differences
homozygosity	Different alleles can be found on both chromosomes of a pair at the same gene locus
phenotype	An organism's observable physical, physiological or behavioral characteristics, being the product of the organism's genes and influences from the environment
polygenic	Multiple genes exert an effect on the same trait
polymorphism	A gene locus where two or more alleles can be observed
population stratification	Systematic difference in allele frequencies between different (sub-) populations (i.e. related to ancestry)

BOX 2 Guidelines for candidate gene and candidate gene x environment association studies, primarily based on editorial policies for evaluation and consideration of manuscripts at Biological Psychiatry (1), Behavioral Genetics/Psychological Science (2) and the Journal of Abnormal Child Psychology (3) as well as some recommendations from the literature. Note that not all of these recommendations are discussed in detail in the paper; for more information see the cited references.

Recommendations on study design, statistical approach and reporting

- Sufficiently *large sample size*[1,2,3]
- Studies are considered[2,3] or given highest priority[1] when an adequately-sized *direct (and independent) replication* is provided in the same manuscript[2] or when a large sample can be randomly split[3]. Thereby, *direct replications* of previously reported results in an independent sample are said to be considered with equal priority irrespective of the outcome (null findings, replication or contradictory finding) when rigorously conducted and adequately sized as demonstrated by power calculations[1,2,3]
- Appropriate *correction of statistical significance* such as taking into account all sources of multiple testing such as different phenotypes, genotypes, covariates and sub-groups[2,3]
- Power estimates need to be provided (in particular in negative studies)[1,3]
- Consideration of *population stratification* is essential and information about *subject ethnicity* is included as well as how it was determined[1,3]
- Following of the *STRTEGA reporting guidelines* (Little et al., 2009) for genetic association studies is recommended[2]

Recommendations regarding selection of the phenotype

- Established *heritability* of the phenotype (Lonsdorf & Kalisch, 2011)
- Clear description of the *definition* and reliable as well as valid *quantification of the phenotype*[1,3]

Recommendations regarding gene selection

- Candidate gene selection needs to be based on strong *biological or positional rationale* or *a*-priori precedents based on the literature[1]
- Candidate polymorphisms selection has to be justified (against other possible choices) and choosing variants with known *functional consequences* strengthens the case[1,3]
- Appropriate *justification on gene modelling* (e.g. recessive vs. dominant or co-dominant model) as well as reporting on all genotype groups for completeness in case a dominant model (i.e. short-allele carriers vs. long-homozygous) is chosen (Dick et al., 2015)
- Analysis of *pathways or candidate regional analysis* is encouraged over single gene studies[1]

Miscellaneous recommendations

- In gene-environment studies, prospective longitudinal designs are more suited than cross-sectional design to rule out *reverse causation*[3]
- For studies of anonymous variants (see glossary) , dense marker coverage (i.e. mapping of the specific region by identification of genetic variants) should be presented and if rare variants are being tested, the same method of assessment should be used in both case and control groups[1]