**Molecular genetics in psychology and personality neuroscience: On candidate genes,
genome wide scans, and new research strategies**

Christian Montag^{1,2*}, Richard P. Ebstein³, Philippe Jawinski⁴ & Sebastian Markett^{4*}

¹Department of Molecular Psychology, Institute of Psychology and Education, Ulm University, Germany

²neuSCAN Laboratory, Clinical Hospital of the Chengdu Brain Science Institute and Key Laboratory for Neuroinformation, University of Electronic Science and Technology of China, Chengdu, China

³C2BEF (China Center for Behavior Economics and Finance), Southwestern University of Finance and Economics, Chengdu, China

⁴Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany

*To whom correspondence should be addressed

Prof. Dr. Christian Montag
Heisenberg Professor
Institute of Psychology and Education
Zentrum für Biomedizinische Forschung
Ulm University, Helmholtzstr. 8/1
D-89081 Ulm
Germany. Tel +49-731-50 26550
Fax +49-731-50 32759
E-Mail: christian.montag@uni-ulm.de

Prof. Dr. Sebastian Markett
Department of Psychology
Humboldt Universität zu Berlin
Unter den Linden 6
10099 Berlin
Germany
Email: sebastian.markett@hu-berlin.de

Despite the substantial heritability estimates for psychological traits, their precise genetic foundation from a molecular perspective remains elusive. We summarize findings and advances from twenty years of research into the molecular genetics of personality and other psychological traits. We describe how the candidate gene approach has – despite its appealing theoretical foundations – often (but not always) failed to point towards replicable associations between genetic polymorphism and behavioral traits. The genome wide analysis (GWAS) approach on the contrary has become more fruitful in recent years and pointed towards reliable genetic associations. GWAS results are currently leveraged to explore gene-behavior associations through genetic correlation and polygenic score prediction which are important steps towards a precision medicine where treatment options are tailored to a patient's individual biology. The GWAS approach, however, faces its own problems when it comes to linking its extensive findings to biopsychological theory. We argue that research strategies from the candidate gene approach can be used to address these issues – given that necessary precautions are taken to avoid the problem of false-positive associations.

1. The status quo in the investigation of the molecular genetics of personality

An integral part of *Personality Neuroscience* seeks to understand the molecular genetics underpinning individual differences. This research endeavor is of importance, as twin studies have demonstrated that a substantial proportion of the variance in individual differences can be accounted for by heritability (about 50%) across a large number of human traits (Polderman et al., 2015). Identifying genetic variations linked to personality is thus a crucial step towards explaining the biological mechanisms underlying individual differences in thought and behavior. Moreover, it is also highly relevant from a clinical perspective towards preventing, diagnosing and treatments of pathological conditions. Biological personality theories have long emphasized the overlap between trait systems at the neural level and brain circuitry involved in clinically relevant behavior, viz. anxiety and amygdala reactivity. Particularly, dimensional models of behavioral disorders and psychopathology often assume that the same genetic mechanisms underlie normal individual variation and more extreme clinical manifestations (e.g. Okbay et al., 2016) suggesting a personality continuum from nonclinical to clinical pathology.

The field of molecular genetics in *Personality Neuroscience* is more than twenty years old. Probably the most relevant starting point has been the publication by Lesch et al. (1996) that linked a genetic variation on the serotonin transporter (*SLC6A4*) in the upstream 5' repeat region (5-HTTLPR) of this gene to anxiety-related personality traits in a non-clinical population. This seminal work stimulated many studies towards replicating the original

findings and extending the role of this repeat polymorphism to correlations in clinical populations, especially neuroticism related traits. However, reproducibility attempts of these findings have only been partially successful (see meta-analysis by Sen et al., 2004; Munafò et al., 2009). This early work by Lesch et al. (1996) is a classic example for the so called candidate gene approach (CGA) in *Personality Neuroscience*, which has been the focus of much criticism in the last years (e.g. Sanchez-Roige et al., 2018). The difficulty with candidate gene studies is also underscored in several reviews: Duncan and Keller (2011) performed a wide review of all published candidate gene–environment interaction studies (N = 103) relevant to psychiatric traits (covering 2000–2009). Although most novel candidate gene–environment interaction studies revealed significant results, only ~25% of replication attempts attained significance. In addition, the authors noted a potential publication bias among replication attempts. Notably, power calculations indicated that even when assuming relatively large effects, the vast majority of studies reporting positive results were based on insufficient sample sizes. Hence, many of the published candidate gene results were thought to be false positives (Duncan, Pollastri & Smoller, 2014; Dick et al., 2015) and the overall candidate gene approach became tainted with doubts about replicability of such studies.

A more detailed look at the candidate gene approach

The candidate gene approach derives hypotheses on genes whose involvement in a certain trait seems probable based on psychopharmacological studies in both humans and other mammals (Montag & Reuter, 2014). The idea to investigate the serotonin transporter gene, for instance, is straight forward, even a ‘no-brainer’, if one considers the simple fact that one of the most widely prescribed group of psychopharmaceuticals for the treatment of depression are selective serotonin reuptake inhibitors (SSRIs) that block the serotonin transporter, thereby upregulating the serotonin levels in the synaptic cleft (Arroll et al., 2005). Animal studies of serotonin also have provided important clues as to what elements of serotonergic networks and what phenotypes might be worth considering in a candidate gene approach (Ren et al., 2018). For example, recent studies on the effects of acute activation of dorsal raphe serotonin neurons have revealed the myriad effects of serotonin on human behavior including reinforcement (Liu et al., 2014), promotion of waiting for delayed reward rather than reinforcement (Fonseca et al., 2015), promotion of anxiety-like behaviors and suppression of locomotion (Urban et al., 2016), and suppression of locomotion without effects on reinforcement or anxiety-like behaviors (Correia et al., 2017).

In addition to hypotheses derived from mechanisms of action of psychiatric drugs, biobehavioral theories on affect and personality are powerful sources for suggestive candidate genes (see Markett et al., 2018): Both Montag & Reuter (2014), but also Montag &

Davis (2018), described how Panksepp's Affective Neuroscience Theory (ANT) can be used to guide researchers in choosing candidate genes of relevance for *Personality Neuroscience*. We provide the reader with a short example. Panksepp observed via electrical stimulation studies and pharmacological challenges in mammals, seven primary emotional systems (Panksepp, 1998; see also Davis & Montag, 2019). These have been mapped in detail with respect to brain anatomy and underlying molecules (Panksepp, 2011). As individual differences in primary emotional systems are robustly linked to the Costa and McCrae's (1997) Big Five Dimensions of Personality (with the exception of Conscientiousness; Montag & Panksepp, 2017a, 2017b), researchers can derive new candidates to study individual differences in the Big Five by applying Panksepp's ANT (Montag & Davis, 2018). For example, it has been demonstrated that opioids have an influence on PLAY behavior in rats (Panksepp et al., 1985). As PLAY might be the evolutionary oldest expression of extraversion, it is reasonable to hypothesize that opioids might also play a role in understanding extraversion (again see Montag & Reuter, 2014). As a result, researchers might select genetic variations of the opioid system (such as the gene *OPRM1* coding for the Mu-receptor; e.g. Fillingim et al., 2005) and try to link it to individual differences in extraversion. But what SNPs should be exactly chosen on opioid relevant genes? Before answering this, we shortly like to introduce a second approach that has become increasingly popular following contentious findings with the candidate gene approach: The genome-wide association study (GWAS) approach.

The genome wide association study (GWAS) approach

The GWAS approach can be considered mostly agnostic/atheoretical, as it does not make use of theoretical guidance in its search for associations between genetic variation and phenotypical traits such as personality. Rather GWAS is a black box strategy and is implemented with no priors. The GWAS approach was rendered possible by modern advances in genotyping technology that enable to genotype several thousand genetic variants simultaneously in each research participant in a highly automated, efficient, and relatively inexpensive manner using specialized oligonucleotide arrays. One benefit of GWAS is that they are capable to discover novel variants, genes, and pathways, which have not been previously proposed. The microarray used by the UK Biobank, for instance, allows for the simultaneous assessment of more than 820,000 variants, which are both single nucleotide polymorphisms (SNPs) and short insertions and deletions (indels, Bycroft et al., 2018). While a subset of these variants was selected based on known associations or their functional role in protein coding, the vast majority of variants was chosen to optimize genome-wide coverage in order to aid genotype imputation. Imputation methods utilize information on linkage disequilibrium from reference samples such as the 1000 genome

project to impute a far larger amount of genotypes with high confidence. The UK Biobank, for instance, achieved a more than 100-fold increase in the number of genotypes by means of imputation and provides around 96 million genetic markers in total (Bycroft et al., 2018). These markers include the vast majority of known SNPs and indels known today (The 1000 Genome Consortium, 2015).

Genome wide association studies (GWAS) make use of mass-univariate testing to assess genetic associations between each genetic variant and a phenotype of interest, which can be categorical (such as a psychiatric diagnosis) or dimensional (such as a personality trait). This mass-univariate approach requires rigorous control for alpha error inflation due to multiple testing. In GWAS, the traditional level of significance $p < 0.05$ for a single test is usually corrected for the number of one million independent genetic variants tested across the genome, resulting in a stringent genome-wide significance threshold of $p < 5E-8$. Given the virtually universal small effect sizes of individual genetic markers for non-Mendelian complex traits, adequate power to detect true effects on such statistical thresholds can only be achieved with huge sample sizes, which makes GWAS a very resource-intensive endeavor. The GWAS approach is also prohibitively expensive (although costs have sunk) and logistically impractical for many laboratory-based tests. For example, functional imaging studies with fMRI using specific tasks are mostly impractical to carry out in tens of thousands of individuals. Similarly, incentivized behavioral economic paradigms (Camerer, Loewenstein, & Rabin, 2004; Montag & Reuter, 2016) such as the Trust Game - the most popular choice in microeconomic studies of human decision making - are hard to implement in large enough numbers to enable GWAS of sufficient power. Often proxies for more detailed psychological profiling are employed to glean information from large surveys that perform often ask only superficial questions. It was only in very recent years that the GWAS approach became fruitful and provided robust genotype-phenotype associations. For a comprehensive introduction into GWAS methodology, see Marees et al. (2018). In the following section, we will review the current state of the art in GWAS approaches to personality.

Genome-wide association studies on personality

The NHGRI-EBI GWAS catalog is a curated online resource that provides direct access to the results of the ever-growing number of genome-wide association studies (Buniello et al., 2019). At the time of writing (July 2019), the GWAS catalog listed 32 studies in the category 'personality trait measurement'. Of these, 29 studies focused on the Big Five personality traits with a total number of 1038 genome-wide significant associations. The number of studies and achieved sample sizes varied across the personality traits, with nineteen studies including data of up to 630,000 individuals for Neuroticism, three and four studies,

respectively, including data of up to 262,000 individuals for Conscientiousness and Openness to experience, one study including data of 17,000 individuals for Extraversion, and two studies including up to 76,000 individuals for Agreeableness. Among the Big Five personality traits, all 1038 genome-wide significant findings refer to the trait Neuroticism. Notably, some variants were reported by more than one study and thus reflect duplicate leads. Other variants may be in close genomic proximity to each other and their alleles are co-inherited (i.e., variants are in linkage disequilibrium; LD). We performed an LD-based clumping procedure by making use of the publicly available 1000 Genomes dataset and found that 337 of these previously reported variants reflect independent associations. We provide a commented shell script on the OSF server to carry out this clumping procedure (<https://osf.io/5tyka/>).

GWAS on neuroticism have been published from 2012 onwards. The timeline of published studies illustrates how a dramatic increase in sample size - together with methodological advancements - has boosted the power to identify variants in genome wide searches. Even though the first GWAS on neuroticism have already made use of meta-analytic strategies to increase sample size to $N = 17,375$ (de Moor et al., 2012) and $N = 63,661$ (de Moor et al., 2015), it was not until the release of the genetic data from the UK Biobank that sufficiently large samples became available to detect SNP associations with genome-wide significance that would replicate in independent samples. Smith et al. (2016) report nine independent SNPs in $N = 106,000$, Okbay et al., (2016) report 11 independent SNPs in $N = 170,911$, Luciano et al. (2018) report 116 independent SNPs (of which 15 replicated) in $N = 329,000$, and Nagel et al. (2018a) report 136 independent loci (implicating 599 genes) in $N = 449,484$. While these studies suggest that a drastic increase in sample size is the appropriate strategy to identify relevant SNPs, the two most recent studies show that genetic and phenotypic correlations can be additionally exploited to increase detection power even further, albeit in a way more cost-effective way (Turley 2018, Baselmans 2019). Here, a total of 263 independent loci for neuroticism was reported in a sample of $N = 2,370,390$ (Baselmans et al., 2019). In figure 1, we summarize the current state of the art of GWAS on neuroticism with a Manhattan plot. The ever-growing number of SNPs associated with neuroticism illustrates the conundrum of the plethora of SNPs indexing common traits and disease. It is improbable that definitive proof of causality, on a par with “Koch’s postulates for genes,” is possible (Chakravarti et al., 2013). Moreover, the polygenic nature of complex traits means that tens to hundreds or more genes contribute to a single trait, making it difficult to evaluate the role of a single SNP variant. We suggest that a common misunderstanding regarding GWAS is that they identify specific genes associated with traits. GWAS in fact simply links genetic loci that can be quite long containing many genes in some cases and are significantly associated with the trait being studied. The linked SNP may be directly involved in gene function in a

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244 What have we learned from GWAS on personality so far?

245 Each GWAS study - no matter whether it is a primary investigation with new data or a meta-
246 analysis of several existing data sets - produces a list of summary statistics. Summary
247 statistics include test statistics and associated p -values for each genetic variant under
248 investigation. Of note, such summary statistics are not only available for the set of variants
249 with genome-wide significance, but also for the larger set of supra-threshold variants that do
250 not meet the strict criteria for genome-wide significance but still carry a fair deal of interesting
251 information. One particularly informative use of these statistics is the investigation of genetic
252 correlations with other traits. Genetic correlations are a quantitative measure of pleiotropy,
253 which is present when a genetic variant affects several traits at once (van Rheenen et al.,
254 2019). Pleiotropy seems to be rule than the exception. Traditionally, genetic correlations
255 have been assessed in pedigree or twin samples, which requires the assessment of several
256 behavioral traits in the same study (e.g. Plomin & deFries, 1979). This limitation has been
257 overcome by the introduction of linkage disequilibrium score regression (Bulik-Sullivan et al.,
258 2015). LD score regression allows researchers to compute genetic correlations between
259 traits across samples based on GWAS summary statistics. This makes it easy to explore
260 genetic overlap between traits, investigate common etiology, establish causal relationships
261 and identify targets for interventions, derive hypotheses on new candidate SNPs, and to
262 boost overall detection power in GWAS meta-analyses (Lee et al., 2013; Maier et al., 2015;
263 Pingault et al., 2018; van Rheenen et al., 2019).

264 Genetic correlation analysis has been applied to the summary statistics from GWAS
265 on personality. All *big five* traits (McCrae & Costa, 1997) have been found to be genetically
266 correlated with each other. All bivariate genetic correlations are positive except for the
267 correlations with neuroticism, which were all found to be negative (Lo et al., 2017). At the
268 same time, all *big five* traits are genetically correlated with several psychiatric disorders
269 which is in line with the conjecture that psychiatric disorders and personality traits share a
270 common etiology and disorders represent an extreme form of otherwise normal individual
271 differences (e.g. Okbay et al., 2016). A closer examination of genetic correlations grouped
272 *openness to experience* with attention deficit hyper-activity disorder (ADHD), bipolar
273 disorder, and schizophrenia, as well as neuroticism with anorexia nervosa, autism, and major
274 depression (Lo et al., 2017). Focusing only on neuroticism, Nagel et al. (2018a) report strong
275 positive genetic correlations between neuroticism and anxiety disorders, major depression,
276 ADHD, anorexia nervosa, and schizophrenia. Strong negative correlations were observed for
277 neuroticism with subjective well-being, and to a smaller extent with IQ and educational
278 attainment. Neuroticism is generally viewed as a super-factor of personality that aggregates
279 a broad range of behavioral dispositions. Self-report inventories of neuroticism therefore

consist of several items that aim at different aspects of the construct. These different aspects seem to reflect a certain degree of genetic heterogeneity. Separate GWAS for each neuroticism item and subsequent genetic correlation analysis between the item-specific summary statistics have revealed that even though all genetic correlations are substantial, their size still varies considerably (Nagel et al., 2018b). Cluster analysis of the item-level genetic covariance matrix has identified two clusters with high within- but low between cluster correlations that are interpreted as *depressed affect* (cluster 1) and *worry* (cluster 2). Genetic correlation analyses with further variables have revealed that these two clusters show differently nuanced intercorrelations with behavioral traits and disorders: *Worry* is, for instance, much more positively correlated with anorexia nervosa and schizophrenia than *depressed affect*. *Depressed effect*, on the other hand, shows a stronger positive correlation with ADHD and stronger negative correlations with educational attainment and IQ than *worry*. Further studies on the genetic correlates of neuroticism have found shared genetic foundations between neuroticism and loneliness (Abdellaoui et al., 2019), and the proclivity to experience pain at different locations of the body (Meng et al., 2019).

Whereas the assessment of genetic correlations through summary statistics can lead to various novel insights, it unfortunately falls short of telling us much about single individuals. It is simply not informative at the level of the individual. But the field still holds on to the promise that genetic research will eventually guide a precision medicine where each patient is treated according to her individual biology (e.g. Chen & Snyder, 2013). For this scenario to come true, it is necessary to translate the group statistics from GWS studies into individual predictions of genetic liability for a certain trait. Polygenic risk scores (PRS) can be computed from GWS data and reflect the polygenic, additive nature of genetic liability by quantifying the amount of “risk variants” in individual genomes (Wray et al., 2007; Purcell et al., 2009; Dudbridge et al., 2013). Individual PRS for a given trait are typically computed as weighted sums of associated genetic variants. This entails the following steps: First, the association strength for each genetic variant is obtained from GWAS summary statistics. Then, the entire genome is partitioned into independent LD blocks based on LD information from a reference panel (“clumping”) and lead SNPs beneath a specified threshold are chosen for each LD block. Then, the number of “risk loci” (i.e. the number of alleles associated with a higher likelihood of the trait under examination) is determined and each locus is weighted by its association strength with the trait in the original GWAS data. An important point is the specification of the p-value threshold. Choosing a very stringent threshold (such as genome-wide significance) can severely reduce predictive power as variants in LD with the GWAS top hits are omitted from the analysis. Choosing a too lenient threshold, on the other hand, can also reduce predictive power because too many false-positive variants are added to the score. Since there is no theoretical argument for a particular threshold, it is common practice

to compute several PRS for each individual based on different p -value thresholds. Empirically, it is often the case that the intermediate thresholds work best. The thresholding procedure can be criticized for lacking a strong theoretical underpinning. On the other hand, however, it allows researchers to calculate PRS for traits for which few or even no genome-wide significant loci have yet been identified.

The PRS for neuroticism was found to predict around 1% of the risk to develop major depression (de Moor et al., 2015), a finding that was later replicated and extended to a broad range of mental health phenotypes such as general anxiety, phobia, panic, and insomnia (Docherty et al., 2018). The PRS for neuroticism is also predictive for subjective age in the elderly (Stephan et al., 2019) and linked to poorer results of a standardized high school exam, lower openness to experience, and lower academic motivation in younger individuals, even though this relationship is not independent from general cognitive ability (Smith-Wooley et al., 2019). A particularly interesting application of PRS for personality is the prediction of treatment response to antidepressant medication. Here, the PRS for *openness to experience* and neuroticism have been linked to the response to selective serotonin re-uptake inhibitors (Amare et al., 2018). Finally, it is of note that the PRS for neuroticism is actually linked to phenotypical neuroticism in an out-of-sample prediction (Nagel et al., 2015). The effect size, however, is rather low (4.2%), which is of no surprise given the low SNP-heritability of personality traits. Even though predictive power has recently been raised substantially to the theoretically expected upper boundary (Turley et al., 2018), the observation by Okbay et al. (2016) still holds that effect sizes are unfortunately too low to be clinically useful. Although speculative at present, this limitation might be overcome when rare variants are added to PRS since it has been recently suggested that SNP-heritability becomes higher once rare variants are considered next to common ones (Hill et al., 2018).

Next to assessing genetic correlations and analyzing PRS, it is of importance to take a closer look at the lead SNPs in GWS results to obtain information on their functional role. This, however, is complicated by the fact that the vast majority (~95%) of GWAS hits fall into non-coding DNA regions (Maurano et al., 2012). Deriving hypotheses on putatively causal variants is therefore not straightforward and requires the comparison of genetic associations with existing data-bases through tools such as FUMA (functional mapping and annotation). FUMA queries 18 databases on the basis of GWAS summary statistics and points towards the most likely causal variants and genes through positional mapping, as well as mapping of expression quantitative trait loci (eQTL) and chromatin interactions (Watanabe et al., 2017). FUMA has, together with multi-marker analysis, implicated 399 genes in neuroticism, which - according to recent estimates - equals to around 3% of all known coding genes in humans (Pertea et al., 2018). Implicated genes are - not surprisingly - predominantly expressed in brain tissue. They play a role in neurogenesis, neuron differentiation, as well as

dopaminergic neuroblasts, GABAergic spiny neurons in the basal ganglia, and serotonergic neurons (Nagel et al., 2018), findings that are consistent with psychobiological models on neuroticism and human personality (DeYoung & Gray, 2009). Because of the genome's LD structure, GWAS top hits do not necessarily need to represent causal variants. Strong associations of lead SNPs can very well be indirect, particularly when they are in strong LD with more than one causal variant. Only about 3% of the lead SNPs for neuroticism fall into exonic regions, however there are more than 17,000 SNPs in high LD with the lead SNPs, including 70 exonic and non-synonymous variants (Nagel et al., 2018). It remains to be tested whether these SNPs are truly causal variants for individual differences in personality.

2. Unifying the candidate gene approach and GWS to study molecular genetics of personality / or: current challenges in molecular psychology

In its quest to unravel the principles of human personality and individual differences, psychological science has been most successful when guided by theory and hypotheses. From its early day onwards, biological personality accounts have emphasized the role of the various major transmitter systems in personality traits (Eysenck, 1947; Gray, 1971; Corr & Perkins, 2006). Such hypotheses have guided valuable investigations that have made use of pharmacological manipulations through drugs or dietary supplementation in healthy human research volunteers and experimental animals. Given this successful tradition, it appeared straightforward to extend this toolbox to molecular genetics and derive candidate genes based on pharmacological evidence ("the pharmacology based candidate gene approach"; pharmacogenetics). The major problem here, however, is the very poor replicability of associations (Munafo & Flint, 2011; Montag & Reuter, 2014). Genome-phenome associations of popular and functional candidate variants (such as 5HTTLPR, BDNF val66met, COMT val158met) have repeatedly failed to replicate in larger samples (Bosker et al., 2010; Border et al., 2019; Jawinski et al., 2016). A further yet related problem is effect size. This of course does not exclusively apply to candidate gene designs but can nevertheless be particularly detrimental of the rate of false-positive findings in such research. The infinitesimal model originally formalized by Fisher (1918) and still valid from today's perspective (Barton et al., 2017; Turelli, 2017) positions that the underlying genetic signal of quantitative traits is highly polygenic with many causal variants of very small effect size. How small is a matter of ongoing empirical examination. But in general, it has been shown that small effects get easily overestimated in small samples, which leads to false-positive findings that of course do not replicate (Schönbrodt & Perugini, 2013; Dubois & Adolphs, 2016). This is not a problem peculiar to candidate gene genetics, since replicability is a general problem in psychology and the life sciences (Ionnisidis, 2005; Open Science Collaboration, 2015). In

light of the ‘replication crisis’, the candidate gene approach has therefore been questioned or even rejected by many researchers in the field. GWS have been proposed as the gold standard in the field up to a point that candidate gene studies have been called obsolete (Duncan et al., 2019).

Current challenges for the GWAS approach

The success of present day GWAS studies is irrefutable albeit it might be argued that GWAS results fail to generate truly causal relationships between SNPs and traits. Ever since GWAS have become sufficiently powered, they have uncovered replicable SNPs, revealed the covariance structure of genetic signals, and most importantly achieved out-of-sample prediction (see the brief review of recent personality findings above). The GWAS approach, however, faces its very unique challenges, which should let us re-evaluate the candidate gene approach instead of refuting it altogether. We should avoid ‘throwing the baby out with the wash’. Several challenges arise from the sample size requirements for GWAS that easily exceed 100,000 and actually approach a million. Such sample sizes can only be realized in large collaborative efforts and by meta-analyses of several large data sets, which inevitably profoundly constrains the assessment of phenotypes. Collaborative data sets typically include a plethora of medical and psychological phenotypes. There is thus only very limited time for the assessment of each data point in order to keep assessment length reasonable for participants. Psychometric measurements usually require several items to capture a construct in depths. Compromising on length and the number of items inevitably reduces the reliability of an assessment, which can only be compensated by increasing sample sizes even further. Very brief assessments may make it easier to quickly achieve a sufficient sample size for meaningful GWAS results. The breakthrough for intelligence, for instance, was achieved by collating “years of education” as a proxy for intelligence across several data sets (Lee et al., 2018; Plomin & von Stumm, 2018). On the other hand, such strategies fall short of capturing a detailed picture of the construct under investigation. Other research on personality traits for instance has shown that the genetic signal differs for several aspects of neuroticism and has revealed genetic associations that would have remained elusive in shorter assessments (Nagel et al., 2015b; Hill et al., 2019). GWAS approaches will thus need to find a way to balance the need for extra large sample sizes and psychometric assessments of sufficient depth. A further problem is that personality psychology has not agreed on a gold standard to assess personality domains. As a result, we are facing heterogeneity in assessment tools across data sets. To a certain extent, the heterogeneity can be ameliorated by harmonizing different assessments across studies (Moor et al., 2015). But in general, it would be desirable to work with the same assessment tools of sufficient length and breadth across all participants in a sufficiently powered GWS design.

Finally, it is currently a major challenge to make causal sense of GWAS results. Almost all GWAS hits imply variants in non-coding and intergenic regions. While there is of course a chance that such variants are causally linked to the phenotype under investigation, it is more likely that they are implied through the LD structure of the genome. If a variant is in strong LD with several causal variants, it is most likely that this variant will be among the first to reach genome-wide significance once statistical power increases. LD information and databases can help to derive lists of non-synonymous variants in coding regions or variants in regulatory regions. But since such variants have not been directly linked to the phenotype in question, they will remain nothing more than new candidate genes until proven otherwise in follow-up studies (Breen et al. 2016). Many of such follow-up studies will be “classic” candidate gene assays, only with the differences that candidates are not chosen based on theoretical considerations and pharmacological evidence (pharmacology based candidate gene approach, *PB-CGA*) but based on data-driven GWAS results (GWAS based candidate gene approach, *GWAS-CGA*). This idea is also highlighted in figure 2. The distinction between *PB-CGA* and *GWAS-CGA* might appear to be trivial, but we maintain that it is essential to emphasize the following point: Candidate gene studies are neither inferior to GWS approaches per se, nor have candidate gene approaches been rendered obsolete by GWS approaches. Both approaches play complimentary roles in the quest to unravel the molecular genetics of personality and other phenotypes. The field just needs to follow due caution to make sure that candidate gene studies are sufficiently powered and properly controlled to avoid the well-known pitfalls of genetic association studies. We will discuss such strategies in the following paragraph.

3. Improving candidate gene studies

(Personality) Psychology has a long tradition in investigating human nature with guidance from clear hypothesis and theory. From this traditional point of view, the candidate gene approach clearly has its legitimacy in the scientific community. But as mentioned throughout this work, we are aware about the problems in replicating many of the genetic associations published stemming from the candidate gene approach over the years (Munafo & Flint, 2011; Montag & Reuter, 2014) - reflecting perhaps the general replication crisis in psychology (Open Science Collaboration, 2015). As a consequence, every researcher has to find solutions to improve genetic association studies. One such solution might be the establishment of molecular genetic research groups or collaborations with local investigators in different areas of the world in order to be able to replicate findings across different ethnic groups. Of note, the power to test for genetic effects differs across ethnic groups, because polymorphism frequencies can vary considerably across ethnicities. Therefore, it is of

importance to have enough power to test for genetic effects in both samples, because the minor allele frequencies often differ. Therefore, sufficient sample sizes at both sides are needed to minimize the likelihood of false positive findings (in our last work by Sindermann et al. (2018) a minimum of about 600 participants at each site was used, but data banks are growing rapidly).

In two recent works we indeed were able to demonstrate same genetic effects in the German and Chinese samples. Observing the same results in such different ethnic groups is *per se* a sign of robustness. In Montag et al. (2017) the TT variant of the functional rs2268498 OXTR polymorphism was associated with lower autistic traits in both samples. In the work by Sindermann et al. (2018) the Met allele of the prominent COMT Val158Met polymorphism was associated with both higher avoidance motivation in the context of trait vengefulness in female German and female Chinese participants. Given the very different cultural backgrounds of Germany and China, as well as differences in minor allele frequencies of SNPs across these ethnic groups, we argue that obtaining the same results strongly suggest that the effects we observe can be potentially extended to populations across the globe. These examples highlight that the candidate gene approach (oxytocin and dopamine genes as targets have been derived earlier by pharmacological studies) still can be used to disentangle the molecular genetic underpinnings of personality, but standards have risen concerning the urgent need to demonstrate independent replication (ideally by other work groups). Moreover, it is of importance to also test the effect of such a SNP in laboratory-based studies going beyond self-report. In line with the above mentioned finding the TT-variant of rs2268498 has also been associated with better performance in an emotion recognition task (Melchers et al., 2013), social perception/implicit learning (Melchers et al., 2015; Melchers et al., 2017), and functional connectivity of amygdala subnuclei (Zimmermann et al., 2018). We suggest that only by testing a genetic variant with a multi-method mix, the effects of a genetic variant on human behavior can be best characterized and understood.

A different replication strategy lies in the attempt to characterize candidate SNP effects by establishing such effects in a theoretically meaningful nomological net of relevant psychological constructs. Instead of just seeking to simply reproduce an association between a given genetic marker and the same phenotype assessed by the same behavioral measure or questionnaire, this approach seeks to associate the genetic marker with different phenotypes. The rationale for this approach is based on the following considerations: There is no gene (or genetic variant) for a certain behavior. Rather, genetic variation affects molecular, cellular, and eventually system-level pathways that produce a given behavior in top down and bottom up levels of interaction. It is therefore highly plausible that two

behavioral phenotypes that are theoretically related and rely on a shared neural resource are also associated with similar genetic variation. This argument is supported by ample evidence from quantitative genetic research that has shown that phenotypically related traits are also genetically correlated, i.e. affected by the same set of genetic factors (Sodini et al., 2018). The equal effect of one genetic variant on many phenotypes is called pleiotropy (see above), and it has been shown that pleiotropy is commonly observed for many genetic variants (Sivakumaran et al., 2011). We have conducted several studies on genetic variation on the DRD2 gene in the cognitive framework of working memory and executive control and linked DRD2 to both visual and auditory working memory as well as executive control (Markett et al., 2010a, Markett et al., 2011b, Markett et al., 2011). This approach is also profitably combined with neural imaging studies, so called imaging genomics. Imaging genomics has been advocated for several years now, particularly in psychiatric genetics where the first-generation GWAS studies failed to observe any associations between psychiatric disorders and individual genetic variants. The idea behind imaging genetics is to circumvent the problem that psychiatric nosological categories are often too broad or heterogeneous to find unambiguous genetic associations. By looking at more narrow neural phenotypes that are actually biological phenotypes themselves, it can also be argued that neural processes are closer to the genetic level in the putative causal chain from genes to behavior and thus more directly affected by genetic variation than psychological constructs. While genetic imaging can be used to study new candidate genes, it can also be applied in the above-mentioned replication strategy to assess whether a gene-behavior association generalizes to an association between the same genetic variation and the neural systems underlying the behavioral trait. With regard to DRD2 for instance, it was shown that the genetic association extends to the neural level by showing associations between basal ganglia morphology (Markett et al., 2013) and structural connectivity (Markett et al., 2017).

Concerning genome wide association studies we argue that they are most informative by revealing new candidates to be further tested in follow up studies towards a deeper understanding of the molecular basis of the phenotype. As mentioned above, the problem of many genome wide scan studies is that they also produce candidates in intergenic regions or identify SNPs, where functionality has not been proven yet. Ironically and as a consequence, we argue that the GWAS approach generates nothing else but new candidates to be tested in GWA - candidate gene studies. Without further testing, it will not be possible to demonstrate how these genetic variations are linked to personality. In this context a new work by Jung et al. (2019) is interesting, where it could be observed that a SNP robustly associated with neuroticism in a GWA study, was again associated with individual differences in anxiety in a smaller sample of the Ulm Gene Brain Behavior Project.

Therefore, we argue that in the future pharmacological based candidate gene approach (PB-CGA; refer to selecting candidates based on pharmacological studies) will be aided by the complementary GWS based candidate gene approach (GWS-BCGA). This idea is also highlighted in figure 2.

Figure 2: Illustration of the idea that results from genome wide scans result in further candidate gene studies. Therefore, candidate gene studies need to be distinguished into *pharmacological based* and *genome wide scan based* candidate gene studies

To summarize, we strongly advocate for viewing candidate genes and GWAS studies as complementary rather than inferior or superior. They are both necessary to understand individual differences in personality – but studies from the realm of PB-CGA need to be improved with respect to a study's design such as proposed above. A further note: GWAS usually only examines SNPs. However, many interesting VNTRs such as MAO-A or the insertion-deletion polymorphisms 5-HTTLPR need to be investigated by sequencing strategies or by classic gel electrophoresis techniques. Such repeat polymorphisms are not picked up in typical GWAS studies using microarrays. The same is true when designing models of gene by environment or gene by gene effects, which cannot be fully accounted for in current GWAS approaches.

559
560 *4. How to choose genetic variants of interest when following a pharmacologically based*
561 *candidate gene approach?*

562
563 In the literature it has been quite obvious that genetic variants are most heavily investigated,
564 when functionality has been proven. This is the case for the “stars” of the neurosciences
565 such as COMT Val158Met (Lachman et al., 1996), BDNF Val66Met (Egan et al., 2003), 5-
566 HTTLPR (Lesch et al., 1996), MAO-A (Sabol et al., 1993) and more recently also OXTR
567 rs2268498 (Reuter et al., 2017). Such information on functionality is of great importance,
568 because it gives the researcher insights into the consequences of a genetic variant on
569 molecular level and from this also first ideas on how the molecular structure differs in the
570 brain according to the genetic make-up of a person. Unfortunately, knowledge about the
571 functional consequences of genetic variations is the exception and for many genetic variants
572 it is completely unclear how such variations are explained on the molecular level in the brain.
573 This is an avenue for future fruitful investigations.

574 If a researcher follows the PB-CGA, it should be mandatory in the near future to genotype all
575 relevant SNPs (Stram et al., 2004) and implement haplotype analysis to investigate the effect
576 of the entire scope of gene variation on a personality trait (Aluja et al., 2018). This would help
577 to describe how strong certain genes or better cluster of genes of a certain molecular
578 pathway impact on a given personality trait. Following a pathway-based approach one could
579 think of the following example: if oxytocin hypothetically is of relevance for a certain trait, the
580 researchers should aim at the investigation of all relevant oxytocin genes such as coding for
581 oxytocin directly (OXT), the oxytocin receptor (OXTR) or CD38 (impacting on oxytocinergic
582 neurotransmission; Ebstein et al., 2012). With respect to polymorphisms being well
583 characterized on a functional level (but also SNPs robustly derived from GWAS), we think it
584 is feasible to study several such polymorphisms in a focused study, as long as the replication
585 issues are taken into account.

586
587 *5. Further ideas to improve genetic association studies*
588

589 At the ISSID conference in Warsaw a discussion was brought to the table arguing for
590 implementing comparable self-report questionnaires in molecular genetic
591 associations/neuroscientific studies across the globe. This would help to standardize the
592 phenotype and presumably minimize noise across studies improving reproducibility of
593 studies. Hence, non-replication then would have nothing to do with often strongly related, but
594 not exactly similar assessed constructs. We understand that every researcher has his/her
595 favorite inventories and that this will not be a problem, as long as one standard inventory as

reference measure would always be implemented. We think it even to be sufficient if such genetic results on this reference measure are only presented in the supplement of an article. In any case such a questionnaire assessing the Big Five needs to possess several characteristics. First, it not only should assess the broad Big Five constructs, but also sub-facets of the Big Five. Second, it needs to have good psychometric properties and third it needs to be readily available in many different languages. Finally, it should not be long, so that researchers cannot dismiss it because of its length. We propose that such a measure could be the BFI-44. Along with self-report measures, new technologies stemming from the field of Psychoinformatics might be helpful to also combine molecular genetic/biological markers with real world behavior (for an introduction see Montag et al., 2016 and Montag et al., 2017).

With the growing importance and knowledge about epigenetics it will be interesting to see if including information on epigenetic methylation patterns in candidate genes will improve the results of molecular genetic association studies. It is well documented that heritability estimates change over life (Plomin & Spinath, 2004), which could be a consequence of changes in the epigenome (Fraga et al., 2005; Wong et al., 2010). It would certainly be worthwhile to account for epigenetic patterns in molecular genetic association studies.

Finally, we point to a new work by Plomin & von Stumm (2018) attempting to disentangle the molecular genetics of intelligence. As one SNP usually only explains a fraction of complex quantitative traits such intelligence/personality, it has been observed that the inclusion of the information of 4.8 million SNPs in a model explains about 20% of the genetic effects observed in twin studies. By having the beta-values from each SNP derived from such a genome wide association studies, it might be even possible for future researchers to conduct experiments again with a small number of participants (but clearly on the genetic side the enormous amount of information would be needed to be included to achieve the highest effect size possible). Given the complex interplay between genetics and the environment, together with epistasis (Montag et al., 2010a,b) and gene by environment effects (Karg et al., 2011), we still argue that from a personality diagnostic view it will be impossible to make accurate predictions on individual level from genetic information, at best only approximate estimates can be achieved (and we are still very far away from such an outcome).

In sum, more than twenty years since the inception of the fascinating quest to unravel the molecular genetic underpinnings of personality, still many challenges lie ahead, but the general polygenetic nature and its complex interplay with the environment are well described.

Author contribution

CM and SM planned the present work and wrote the manuscript together. Both RE and PW revised this original version of manuscript in detail. All authors approved the final version of this manuscript.

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Conflict of Interest.

There is no conflict of interest. Outside of the scope of the present paper, Dr. Montag has received (to Ulm University and earlier University of Bonn) grants from the German Research Foundation (DFG) and the German Federal Ministry for Research and Education. Dr. Montag has performed grant reviews for several agencies; has edited journal sections and articles; has given academic lectures in clinical or scientific venues or companies; and has generated books or book chapters for publishers of mental health texts. For some of these activities he received royalties, but never from the gaming or social media industry. Dr. Montag mentions that he is part of a discussion circle on social media and democracy at Facebook. In this context, he receives no salary for his activities from Facebook, but his travel costs have been reimbursed. Within the scope of the present paper, Dr. Montag receives funding for a project on digital phenotyping from Mindstrong Health.

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