The role of gene x social environment interactions in psychiatric disorders

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Abstract

The role of genes in psychiatric disorders (PDs) has long been suspected based on the observation that such diseases often run in families. However, genes cannot account for all risk in the development of PDs as environmental factors, such as stressful life events, also affect the risk of developing PDs. Social environment is of particular interest, because the variation in the quality of the social environment created by 'the genotype' of a person is subject to selection and evolution and it is relatively easy to manipulate, offering the opportunity for treatment or prevention of PDs. This thesis looks into the interaction between genes and social environment in psychiatric disorders. In ADHD, depression and hyper-aggression these interactions have a major effect. Interestingly, most of the genes mentioned in this paper interact with social environment in a 'for better or worse' manner. Instead of being just risk genes in an adverse environment, children carrying these genes and living in a nurturing environment grow up to have less symptoms of psychiatric disorders. These children even benefit most from parent intervention training. The phenomenon of 'indirect genetic effects', behaviour of others (in part due to their genetics) affects our own behaviour, is a very possible way in which small gene expression and social environment alterations can influence the development of PDs. Because g x se interactions play such an important role in the development of PDs, I recommend to look further into these interactions, with a strong emphasis on the social environment and its evolution, instead of looking at them in an isolated fashion. Insight in these interactions could lead to better treatment and intervention/prevention, giving way to personalized medicine. More importantly, adaptation of the (social) environment to the genotype could give an even higher advantage than manipulating the genome or administrating drugs.

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Introduction

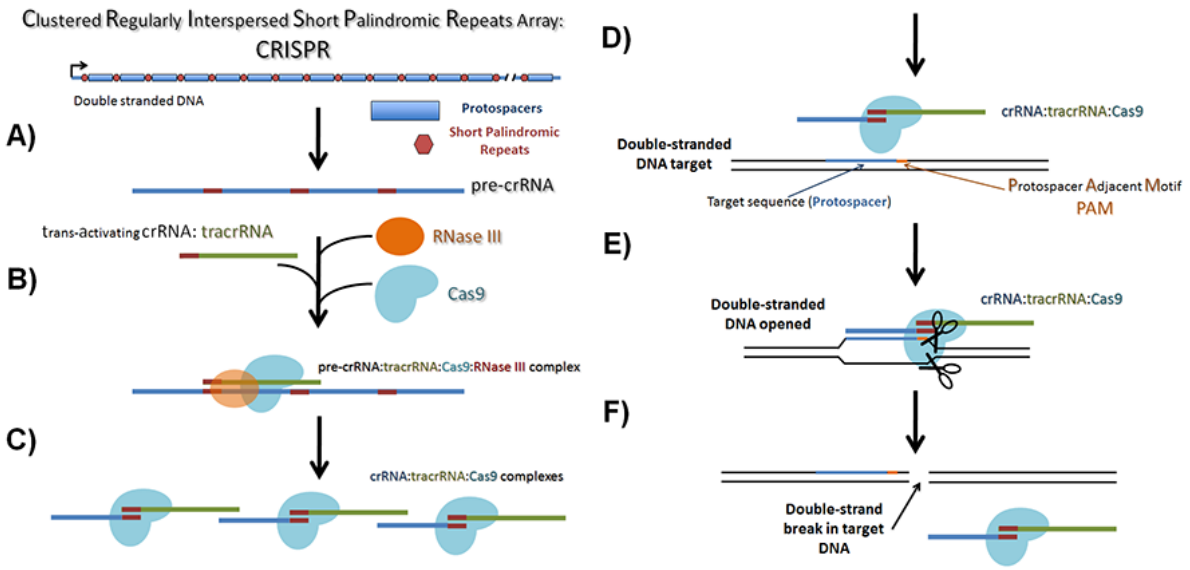
Psychiatric disorders (PDs) have a major impact on personal life and society. Mental illnesses are the leading cause of disability adjusted life years (DALYs) worldwide. This accounts for nearly $2.5T per year of healthcare costs globally, with a projected increase of $6T by 2030 (WHO, 2010). In the past few decades considerable efforts have been poured into investigating the nature and causes of these illnesses, in the hope of finding treatments. Unfortunately, an insignificant amount was fruitful enough to reduce the prevalence of these diseases (Sullivan et al., 2012). The molecular aetiology of most common psychiatric disorders still remains elusive, although in some cases genetic mutations are the original basis for disease. Bipolar disorder, schizophrenia and autism have an estimated heritability, or genetic contribution to the phenotypic variation, of 80->90 percent (Burmeister et al., 2008). Genes regulate the cells of the human body by being the blueprint for proteins. However, when a mutation occurs in a gene the corresponding protein sometimes doesn't function properly anymore, homeostasis in the body can be distorted and this can lead to disease. Heredity of a disease can give insights into what genes are involved and, subsequently, knowing about these genetics can give a way into the molecular basis of this disease. With the development of better genetic research methods new avenues for investigating disorders have opened. The hope is that, with new and old methods combined, underlying pathologic mechanisms can be determined and psychiatric disorders can be treated by directly targeting these mechanisms through pharmacological or genetic manipulation (Sullivan et al., 2012).

Genotype

Extensive Genome Wide Association Studies (GWAS) have revealed a large amount of genetic variants associated with psychiatric disorders in human populations. This means that not one but multiple, possibly synergizing, genes are involved in the development of PDs. The small additive effects of ~30 genes could add to the likelihood of developing a psychiatric disorders (Collins & Sullivan, 2013). Unfortunately, current genetic methods focus solely on single gene treatment and we are still quite incapable of treating a complex of synergizing genes. Therefore, for now, we need single isolated genes of large effect to have a chance at successful treatment.

Few unique specific gene effects have been identified for most psychopathology. One of the exceptions is the dominant autosomal Huntington's disease (HD). HD is caused by an abnormally repeat in CAG sequence in the Huntingtin gene (HTT) which encodes a pathogenic glutamine expansion in the Huntingtin protein (Kay et al., 2014). These abnormally long proteins form aggregates which lead to neuronal degeneration in the basal ganglia and cerebral cortex. The latter is the cause of the dementia and personality changes most Huntington patients experience (Bear et al., 2007). Because most patients are heterozygous for this repeat an attractive method for treatment would be to target this repeat selectively, so the 'healthy' allele can take over (Kay et al., 2014). With the possibility to use CRISPR/Cas9 nuclease (type 2 CRISPR mechanism) in an early embryonic stage this treatment is no longer science fiction (see Textbox 1 for details).

Textbox 1. Mechanism of CRISPR



CRISPR DNA is translated into a crRNA-tracrRNA-Cas9 complex, which recognizes a target DNA sequence (for example the abnormal huntingtin repeat). The Cas9 protein will then remove those selected pieces of DNA (Cong et al., 2013). (Addgene)

Another example of a single gene effect can be found in early onset Alzheimer's disease (eoAD). Three dominant autosomal genes are mutated in eoAD: the gene that encodes for the amyloid beta precursor protein (APP), PSEN1 and PSEN2 (Sullivan et al., 2012). Although no treatment is currently available, it is thought that all these mutations cause an abnormal breakdown of APP which leads to neurofibrillary tangle formation and, through that, to neurodegeneration (Bear et al., 2007).

Finally, in Rett's syndrome (a disorder in the autism spectrum) (RTT) mutations in the X-chromosomal MECP2 gene have an exceptionally high penetrance (Sullivan et al., 2012). 90-95 percent of screened RTT patients show *de novo* pathogenic mutations in this gene. MECP2 encodes for a methyl-CpG-binding protein, which is a regulator protein in the development of the nervous system (Williamson & Christodoulou, 2006).

Except for these examples, no such clear cut evidence for a cause-effect relationship between a single gene and a disorder is found in other psychiatric disorders. All these disorders seem to be a product of gene complexes in which each mutated gene contributes a tiny bit to the overall pathologic pattern (Flint et al., 2010).

Environment

It has long been appreciated that genes are not the sole contributors to phenotypes, but that the environment also has a major influence. For instance, being born in late winter/early spring increases the likelihood to develop schizophrenia, which is known as the seasonality effect. It is argued that this may be because the second trimester of pregnancy (critical for fetal brain development) takes place about the same time winter flu season arrives. Toxins produced by the virus or antibodies from the mother could cross the placenta barrier and attack fetal cells. On the other hand, children born in the summer, with a peak in July, show a significantly higher incidence of suicide. It is unknown why and how this effect is present (Carlson, 2014).

The implication of toxins in PDs is also present in substance abuse (alcohol, drugs* and a trend for tobacco) which is associated with an earlier age of onset in HD (Byars et al., 2012). Research done by Simonin et al. (2013) showed similar results for caffeine consumption greater than 190 mg/day, although a causation relationship was not determined.

Furthermore, research suggests an association between prenatal smoking and multiple behavioural

*drugs: amphetamines, cocaine, inhalants, heroin, LSD and marijuana. These drugs were considered together and separately (all associations significant).

disorders, including attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (antisocial behaviour). Research also indicated that there was a dosage-dependent relationship between second-hand postnatal tobacco smoke and the development of ADHD in young children. These effects can persist into adolescence (Zhou et al., 2014).

Genes x environment

To make matters even more complex, environmental factors could have an effect in combination with a specific genotype causing phenotypic plasticity. Environment can, for example, alter the epigenetics and thereby influence the way genes are expressed (Rutter, 2007). Evidence comes from multiple studies looking into different clinical pictures.

Children born in summer and spring (short photoperiod during pregnancy) with a dopamine receptor D4 seven-repeat polymorphism (DRD4 7R) had a higher risk of getting ADHD than children without this repeat (control). Yet, DRD4 7R children born in winter and autumn had a much lower risk of getting ADHD than the control group (Seeger et al., 2004).

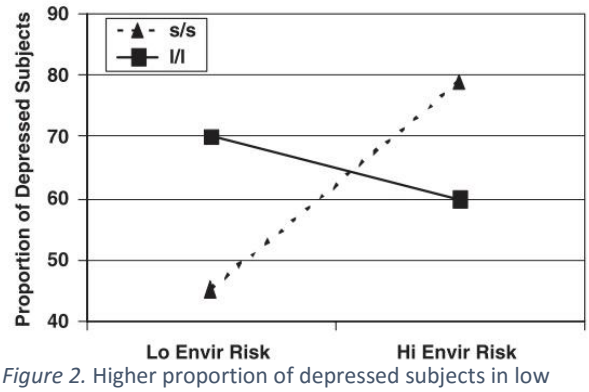


Figure 2. Higher proportion of depressed subjects in low environmental risk group and HTTLPR L/L variant. Also a higher proportion of depressed subjects in high environmental risk group and HTTLPR S/S variant. (Eley et al, 2004)

Comparable results were found investigating the role of DRD4 gene variants and prenatal smoking on ADHD. Children with the 7R allele were more vulnerable to the adverse effects of prenatal smoking than others without this repeat. Interestingly, these 7R children were least likely to show symptoms of ADHD when they were not exposed to this smoking (Fig. 2) (Pluess et al., 2009). In both previously mentioned studies on the DRD4 7R allele both factors (genotype and environment) did not pose a risk per se for the development of ADHD.

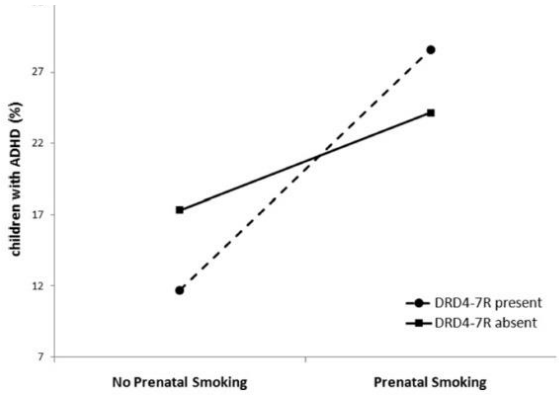


Figure 1. Higher percentage of children with ADHD when prenatal smoking occurred and DRD4-7R variant is present. A lower percentage of children with ADHD when no prenatal smoking occurred and DRD4-7R variant was present. (Pluess et al., 2009)

Caspi et al. (2003) found that people with the S/S or S/L variant of the serotonin transporter promoter region (5-HTTLPR) had an increasing risk for major depression with increasing number of stressful life events (SLE). This is exactly what the diathesis-stress model would predict. This model hypothesizes that how prone a person is to develop a psychiatric disorder, is determined by his/her genetic vulnerability (presence of risk genes) and the amount of adverse environmental factors (SLE's). However, when these people encounter only a few or none SLE's they function much better than the ones with an L/L variant (Fig. 3).

The findings mentioned above indicate that some genes are better called plasticity genes instead of vulnerability genes, supporting the differential susceptibility hypothesis (Belsky, 1997; Belsky, 2005; Ellis & Boyce, 2008). This theory proposes that children with these supposed risk genes are more prone to develop disorders in an adverse environment, but will flourish in a supporting environment.

Social environment

However, it should come as no surprise that one of the most important environmental factors is our social environment. Studies in prisons, in which solitary confinement (SC) is a standard, found disturbing results. Within 7 days a prisoner in SC can exhibit changes in brain activity, which in the long run can lead to depression, memory impairment, phobias and personality changes (Kelsall, 2014). This study suggests a

serious impact of withholding social interactions on human well-being.

Indeed, in all phases of life we are engaged in complex and strong social structures. Research has shown that the caregiving environment can be an important factor in the development of externalizing behaviours like ADHD. For example, if parents exhibit negative early caregiving (insensitivity and low responsiveness), their children are more at risk for developing ADHD (Nikitopoulos, 2014).

Since genes can interact with the environment to influence the phenotype, it is not unthinkable that genes can interact with social environment as well. There is even evidence that genes of others can influence our phenotype through a process called indirect genetic effects. This is of particular interest because the variation in the quality of the social environment created by 'the genotype' of this other person is subject to selection and evolution (Wolf et al., 1998). Knowing about g x se can help us understand the underlying aetiology of psychiatric disorders and can give guidance in the search for treatments. Since genes and (social) environment are highly affected by each other, indicating that there will not be a universal cure for one sole psychiatric disorder, research should focus on personalized treatment for psychiatric disorders. This thesis will therefore investigate the interaction between genes and social environment on psychiatric disorders, in the context of ultimate and proximate causes. This review focusses on g x se interactions in ADHD, depression and hyper-aggression.

Gene x social environment interactions in psychiatric disorders

ADHD

Attention-deficit/hyperactivity disorder (ADHD) is the most common behavioural disorder found in early childhood. It is characterized by symptoms of inattention, hyperactivity and impulsivity that last at least six months (according to DSM-5). ADHD is highly heritable, with a heritability ranging between 75 and 91 percent, which strongly indicates the involvement of a genetic component (Carlson, 2014). Of course, there is the possibility that not all heritability can be accounted for by known genetic factors, this is known as the phenomenon of 'missing heritability' (See Textbox 2 for details).

Medication used to reduce symptoms of ADHD all target the dopamine pathway, either by being a dopamine reuptake inhibitor (Ritalin) or an indirect dopamine agonist (amphetamines) (Carlson, 2014). Dopamine belongs to a family of compounds called the monoamines. Norepinephrine, epinephrine, serotonin (5-HT) and histamine also belong to this system. Most of the neurons producing monoamines are those located in the brain stem, which project throughout widespread regions of the brain, stimulating or inhibiting those brain functions. It is not unthinkable that alterations in this system, with such broad ramifications in nervous system functioning, could influence the severity of the ADHD symptoms. The dopamine pathway, for example, is involved in attention, planning, learning and reward/addiction. ADHD symptoms like inattention and impulsivity can be easily linked to these functions of the dopamine pathway. The importance of this pathway is further stressed by the effect medication affecting the dopamine pathway has on the exhibition of ADHD symptoms. Another candidate is the serotonin pathway because of its implication in the regulation of mood and pain and in the control of eating, sleep and arousal (Carlson, 2014). Although a clear connection can be drawn between the normal functioning of the monoamine pathway and ADHD symptoms, it is important to know if this is a causal relationship.

Evidence for such a relationship came from a study in 7 year old boys showing more ADHD symptoms when carrying a gene variant coding for low activity of monoamine oxidase-A (MAOA). In addition, social environment played a role in the likelihood for developing ADHD as well; more symptoms were observed when they were victims of abuse. Conversely, if they did not experience physical abuse in early life, they exhibited fewer problems compared to boys with the high activity variant (Kim-Cohen et al., 2006). Caspi et al. (2002) found comparable results for the low-activity variant in combination with childhood maltreatment for anti-social behaviour, which is commonly associated with ADHD. These results suggest a role for the MAOA gene in ADHD, but also an interaction between MAOA genotype and social environment in risk for developing symptoms.

Textbox 2. Missing heritability

Heritability is the percentage of phenotypic variance due to genotypic variation in a population. Using GWAS heritability is tried to be explained by finding loci that are involved with the disease. However, not all heritability can be attributed to the found gene variants, they explain only a small proportion of the variance in phenotype. This mystery in human genetics is called 'missing heritability'. The cause for this could be that there are still loci to be discovered explaining the heritability. Another cause could be that the estimated heritability is too high, creating 'phantom heritability'. Genetic interactions can be an explanation of this overestimation (Zuk et al., 2012). Other scientists argue that evolution acts on every phenotypic variation that is stable over generations. Therefore heritability should be divided in a genetic and a non-genetic component, like epigenetics, parental effects, culture and environment (individuals can modify their environment and subsequently alter the selection pressures acting on them) (Danchin et al., 2011). All of these components can interact with each other, possibly producing indistinguishable patterns of transmission from genetic inheritance, resulting in a higher estimated heritability.

Currently heritability is statistically measured by the correlation between phenotypic resemblance and genetic relatedness (inheritance of identical genes leads to the expression of identical phenotypes). Yet the expression of the phenotype is influenced by all the above mentioned factors. Existing methods of measuring heritability should thus be extended with measures of non-genetic components (Danchin et al., 2011).

Concerning the serotonin pathway, a study done in homozygotes for the short 5-HTTLPR allele found more persistent ADHD whenever they had experienced an adverse early environment, compared to individuals carrying the L/L genotype. Interestingly, they showed less persistent ADHD when they didn't encounter an adverse early environment in childhood (Retz et al., 2008), meaning this interaction could be for better or for worse, depending on the experienced social environment.

More research confirms the importance of this g x se interaction. Van der Meer *et al*. (2014) investigated the role of the S/S 5-HTTLPR genotype in interaction with psychosocial stress in mediating ADHD. Indeed they too found a more positive association between severity of ADHD in adolescents and the amount of experienced stress in S-allele carriers than L-allele homozygotes (van der Meer et al., 2014). In a subsequent study they tried to uncover the underlying mechanism for this effect. Since both 5-HTTLPR and stress can affect brain maturation and ADHD is associated with a delay in maturation, van der Meer *et al.* (2015) looked at 1) the interaction between 5-HTTLPR genotype and stress exposure on grey matter volume and 2) which brain regions are involved with this interaction on ADHD severity. Results showed that there was a more negative association between stress and grey matter volume in S-carriers, compared to subjects with a L/L genotype. Also they found two clusters (1; anterior cingulate and paracingulate gyrus and 2; frontal pole) that had a stronger positive correlation, in S-allele carriers compared with L/L homozygotes, between stress and severity of ADHD symptoms that could be explained by less grey matter volume in these frontal regions. These particular regions play an important role in cognitive/executive control (i.a. impulsivity suppressing), including control over the amygdala. Research shows a reduced activation of the prefrontal region in people with ADHD and the symptoms match those encountered in patients with prefrontal damage (Dickstein et al., 2006; Carlson, 2014).

Even more intensely studied is the dopamine pathway. Since the importance of this pathway in ADHD was first recognized due to the effect medication affecting the dopamine pathway has on symptom severity, looking into this system is suspected to give promising insights in the aetology of ADHD.

One of these studies looks into the interaction between the dopamine transporter gene (DAT1) and psychosocial deprivation in causing ADHD symptoms (sADHD). Results show that exposure to extended periods of deprivation, in interaction with a DAT1 10-repeat haplotype, was associated with higher levels of sADHD compared to subjects with another DAT1 genotype. The kids were tested at multiple ages and the effects grew stronger from childhood to mid-adolescence (Stevens et al., 2009).

Most other research focusses on the role of the dopamine receptor D4 (DRD4). Greater levels of externalizing behaviour, which is negative behaviour directed toward the external environment, (when age of children ~3 years) were found when greater maternal insensitivity was observed at the child's age of 10 months. This effect was only found for carriers of the 7-repeat (in exon 3) DRD4 allele (DRD4-7R). Children with the DRD4-7R showed least problems when mothers were observed to be highly sensitive, compared to children without this repeat (Bakermans-Kranenburg & van Ijzendoorn, 2006). The same was found for sensation seeking behaviour (Belsky et al., 2009). Interestingly, Nikitopoulus et al. (2014) discovered that the effects of early maternal care are persistent until adulthood.

Not only are variations in tandem repeat found to be linked to exhibition of sADHD, variation in the number of repeats in the promoter region of the DRD4 gene are also investigated. Again an interaction between inconsistent parenting and DRD4 genotype was found to be a predictor of ADHD symptoms. Children with the risk allele (long repeat in the promoter region) that also encountered inconsistent parenting showed higher levels of sADHD compared to children with low risk alleles (Martel et al., 2011).

Although there are strong indications that DRD4 genotype and social environment interact in the development of ADHD, it is still unclear what the underlying mechanisms are. It is hypothesized that children with the DRD-7R are either less or more sensitive to sensory and reward stimuli. Therefore, the behaviour of these children may be more dependent on the behaviour of their parents than children without the repeat (Nikitopoulus et al., 2014).

Depression

Major depressive disorder (MDD) is characterized by continuous depression or episodes of depression, both always without mania. Research found that people with affective disorders die 28.8 times more of suicide than the general population. Also it is one of the leading causes of disability, with a prevalence of 3 percent in men and 7 percent in women (Carlson, 2014). The heritability of MDD is estimated at 37%, but is likely to be substantially higher (Sullivan et al., 2000).

Since SSRI's are the best working medicine for depression currently known, most research focusses on the serotonin pathway. Again research from Caspi et al (2003) showed a link between MAOA gene variants and children's sensitivity to maltreatment. Subsequently they found that adult depression, in high income countries, was significantly moderated by 5-HTTLPR genotype in interaction with childhood maltreatment. Carriers of the S-allele were more prone to develop depression in adulthood than L/L homozygotes. The short allele is found to be less efficient in promoter transcription than the long allele.

Rocha et al. (2015) repeated the study of Caspi et al. (2003) with the exception of using subjects from middle and low-income countries. They found similar results. What is particularly interesting is that both studies show that subjects with the S/S 5-HTTLPR genotype are less at risk for developing depression when they did not encounter childhood maltreatment, compared to subjects with a L/L genotype.

Furthermore, research from Fisher et al. (2013) looked into the interaction between different forms of childhood maltreatment and HTTLPR genotype in unipolar recurrent depression. They found a significant association between sexual abuse in childhood and depression in S-allele carriers. A weaker interaction was found for physical abuse, but this didn't remain significant after correcting for multiple testing. These results imply that there is a difference in impact that different forms of maltreatment have on depression.

Although there are strongly convincing results for a g x se interaction in depression a meta-analyses reviewing all research investigating the interaction of 5-HTTLPR genotype and SLE's in depression found inconsistent results. Some adding evidence for a g x se interaction and some countering it. Different reasons were proposed to this discrepancy, among them the use of different stressors and heterogeneity of study design (Rocha et al., 2015). Which is confirmed by the different results for variance in childhood maltreatment Fisher et al. (2013) found. In general, the results for an interaction with childhood trauma instead of SLE's are more consistent though. This is why researchers recognize the importance of highlighting what difference choosing a particular parameter could make.

In spite of the abundant attention given to the serotonin pathway, there is also evidence for other genes involved in depression. For example, the ADCYAP1R1 gene that encodes the receptor for pituitary adenylate cyclase-activating polypeptide (PAC1). This protein plays an important role in the stress response. Results indicate an interaction between trauma-exposed women living in high-crime neighbourhoods and women having 2 copies of the C-allele of this gene in risk for depression. When women had 2 copies of the C allele, but were living in a low-crime neighbourhood, they had a lower risk of having symptoms of depression (Lowe et al., 2015).

Despite all the ongoing research, it is still unknown what the exact cause of depression is. The University of California - Los Angeles (UCLA) has taken it upon itself to support research looking to understand the origins of depression. Earlier GWAS studies showed no significant results (Flint & Kendler, 2014). Conversely, a GWAS done in 2015, identifies two loci contributing to a risk for MDD, both on chromosome 10. One of these loci is near the SIRT1 gene. This gene encodes for NAD-dependent deacetylase sirtuin-1, which is an enzyme that deacetylates proteins that play a role in cellular regulation. The other locus lies in an intron of the LHPP gene (CONVERGE consortium, 2015). Research published earlier describes a significant linkage between LHPP and a polymorphism in the gene encoding for the serotonin receptor 1A (HTR1A) in MDD. The products of these genes could interact with each other in the pathogenetic pathway of MDD or they could contribute in two different pathways that both are disrupted and synergize to cause MDD (Neff et al., 2009).

There are actually many indications from GWAS studies that depression is a highly polygenetic disorder, in which each gene accounts for a small risk effect. Indeed, the Netherlands Study of Depression and Anxiety (NESDA) showed that polygenic scores interacted with childhood trauma in an increased risk for depression. Unfortunately, it didn't in another sample (RADIANT UK). However, in the same study done using the RADIANT UK sample, a significant correlation was found between polygenic score in depression and SLE's. (Mullins et al., 2016). These inconsistencies could be because of a difference in experimental design; the NESDA used subjects with episodic depression and the RADIANT UK study used subjects with recurrent depression. On the other hand, there's no arguing that these results strongly indicate a contribution of g x se interactions in risk for depression.

Hyper-Aggression

Aggressive behaviour is exhibited by almost all animals for reproduction, self-defence or threatening. In the physical control of aggression neural circuits in the brainstem, which are under the control of the amygdala and hypothalamus, are implicated (Carlson, 2014). Studies in cats indicate a possible role of the dorsal PAG (periaqueductal grey matter) in linking the amygdala and hypothalamus to the actual execution of defensive rage (Greff & Siegel, 2001).

The heritability of aggression is estimated at 50 percent (Provencal, 2015). No single genes causing aggression have been identified yet, with one exception. In a Dutch family repeated episodes of aggressive and violent behaviour occurred in eight males (out of 20 males in sibship). Genetic mapping showed a loss-of-function mutation in the gene encoding monoamine oxidase enzyme (MAOA). This enzyme metabolizes serotonin, dopamine and norepinephrine (Brunner et al., 1993). More evidence for the involvement of the monoamine system comes from the fact that administration of serotonin agonists (fluoxetine) in humans seems to manage aggression problems (Coccaro & Kavoussi, 1997).

Furthermore, hormones can be implicated in aggressive behaviour as well. Androgens modify the early development of the brain and sensitize neural circuits involved in aggression for testosterone. In addition administration of testosterone for a longer period induces aggression in castrated rodents (Carlson, 2014).

Again the mono amine system has been thoroughly investigated. A study done in adolescent boys shows that boys carrying the low MAOA-activity allele and experiencing psychosocial risk engaged in more criminal behaviour (i.e. violence), compared to boys not carrying this allele. Boys with this allele and no experience in psychosocial adversity exhibited less criminal behaviour. Other research done in males and females with the low MAOA activity allele and childhood maltreatment show similar results in levels of aggression. These effects were seen from childhood to adolescence to adulthood (Belsky et al., 2009).

The above mentioned results show a correlation but not a cause effect relationship. To ensure the proper estimation of causality an experimental manipulation study is a necessary means. Gallardo-Pujol *et al.* (2013) used cyberball software (virtual ball-toss game) to let male subjects feel ignored and socially secluded. They looked at whether participants had a low activity or high activity MAOA allele and measured their level of aggression when they were excluded or not. When men with the low activity MAOA allele were socially excluded, they showed more aggressive responses than men with high activity MAOA alleles. When subjects were socially included, there was no difference between the two alleles.

Evidence for the involvement of serotonin comes from experimental manipulation done in rearing environment macaques. It showed an interaction between environment and a polymorphism in the HTTLPR gene on 5-HIAA concentrations. This effect was only seen in peer-reared monkeys with the S-allele. These peer-reared macaques were highly reactive and aggressive due to the early differential rearing environment. This interaction is particularly interesting because rearing of the mother diminishes the low-activity effect of the S-allele on serotonin metabolism and reduces aggressive behaviour development (Provencal et al., 2015).

It is hypothesized that epigenetics play an important role in the interaction between genes and environment in the development of disease. This is mostly because epigenetics can be influenced by external factors and can induce (ir)reversible changes in DNA transcription at any moment in life. Pathways of interest in epigenetics in aggression are the serotonin system, HPA axis and immune system. As earlier mentioned serotonin has highly complex widespread connections with other systems like the HPA axis and immune system. The HPA axis is involved in regulating the stress response. Research in chickens injected with a high (higher than endogenous levels) dose of cortisol in ovo, showed alterations in HPA axis and serotonin system, leading to an increase in aggressive behaviour. Other research showed that cytokine production in early childhood could, probably through epigenetics, lead to alterations in brain development and influence

sensitivity to, for instance, the serotonin and immune system (Provencal et al., 2015). Figure 3 proposes a possible pathway for the above mentioned interactions. These findings suggest even a role for maternal (social) stress in influencing behaviour in her offspring (Provencal et al., 2015). This could even go back one generation more in humans, since oocytes are already developing in the female offspring when they are still an embryo. It would be interesting to look into these maternal effects on offspring and even their progeny.

Indeed, an unbiased genome wide approach showed multiple differentially methylated genes involved in aggression. Amongst others, genes encoding the serotonin receptor 1D, a dopamine transporter and compounds associated with cytokine signalling and the HPA axis (only in woman) were found to be differently methylated (Provencal et al., 2015).

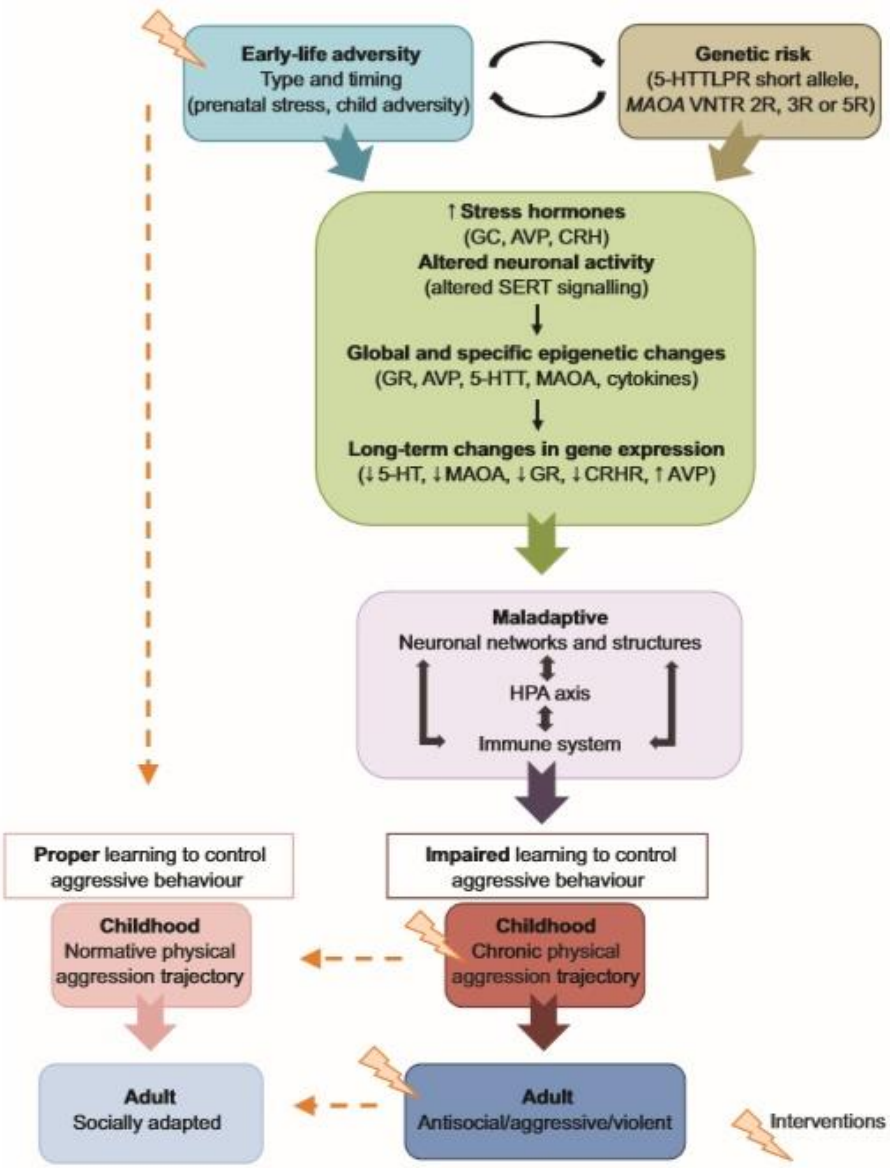


Figure 3. Possible pathway of how genetic risk and childhood adversity could interact in causing aggression in adulthood. Also shown are the possible interventions to lead this pathogenic pathway to an ultimately good end. (Provencal et al., 2015)

Although not much appreciated yet, some research is done on the role of the DRD4 gene in aggression. Schlomer *et al.* (2014) showed a significant interaction between high parental hostility and the DRD4-7R allele carriers in developing aggressive behaviour. Carriers of the 7 repeat allele showed an increase in aggressive behaviour over time, whereas non-carriers did not. These adolescents with the repeat also showed a decline in aggressiveness over time when confronted with low parental hostility. Intervention with PROSPER showed the steepest decline in aggressive behaviour over time in carriers. PROSPER is a preventative intervention project and targets substance abuse and aggressive behaviour problems.

Discussion

The studies mentioned in this thesis all give abundant evidence of an interaction between social environment and genetics in the development of psychiatric disorders. The consequence of this knowledge is that genetic and environmental factor should be studied in context rather than in isolation. Most interesting is the fact that subjects with genetic risk do worst in an adverse environment but benefit most from a supportive environment. This corresponds perfectly with the differential susceptibility theory. The fact that social environment can influence the 'outcomes' of risk or plasticity genes is important in three ways:

- Firstly, manipulation of the social environment could function as a method for treatment and prevention.
- Secondly, the differential susceptibility theory suggests that individuals shouldn't all be treated the same way. A treatment that works for one, could have even worse effects on others. A solution to this problem is personalized medicine. Personalized medicine aims to combine personal health data to prevent, diagnose and treat more effectively. However, to realize this, critics foresee a lot of obstacles to overcome from the discovery of aetology of a disease to analysis of datasets to incorporating this information in healthcare in the clinic. More research should be done on how personalized medicine could become reality (Alyass et al., 2015; Dudley et al., 2015).
- Thirdly, social environment is subject to evolution. Understanding the way social environment has evolved in interaction with genes could provide useful information about underlying pathology. Darwinian medicine or evolutionary medicine looks into the evolutionary history and adaptive value of any given phenotypic trait. It could be the case that disorders in the modern life society were of adaptive significance in earlier environments (Brüne et al., 2012).

In the following sections these implications will be discussed.

Proximate implications: Advice for healthcare

Adjusting the social environment could possibly help prevent psychiatric disorders or in any case decrease the level of symptoms exhibited. Evidence for the effect of intervention comes from variant studies. Bakermans-Kranenburg *et al.* (2008) showed that intervention (video-feedback provided to mothers of 1-3 year olds with ADHD) improved the behaviour of children carrying the DRD4-7R allele the most when mothers showed the most improvement in parenting. In a post-treatment follow up study an experimental stressor was administered and salivary cortisol measured before and after administration. DRD4-7R children reacted less to this physiological stressor when their mothers were assigned to the experimental group and most if their mothers didn't get the parenting intervention. Another study showed that a combination of parent training and social skills training gave better results than getting either one of these trainings. Social skills training is particularly interesting because children with ADHD often have interpersonal difficulties. They are rated more negatively by peers and are therefore more rejected by peers. This can result in an increase in ADHD symptoms (Chronis et al., 2006).

Even children with autistic disorder, which is characterized by a failure to develop normal social relations with other people, benefit from a 20-week education program including skills training (behaviour management) for parents (Tonge et al., 2014).

Provencal et al. (2015) propose that since alterations in epigenetics are potentially reversible by environmental intervention, social intervention or drugs at different time points in the development of the brain could possibly reverse the psychiatric disorder phenotype. This intervention could reset the dysregulated system and give rise to new non-disorder connections, which in turn could result in easier learning of 'normal' behaviour. The earlier these interventions are done the more effective they likely are. It would be best to alter the systems before the neuronal network and structure development and long-lasting epigenetic alterations are established.

Social intervention is one way to handle a disorder if it is still developing or already developed. The earlier mentioned CRISPR, on the other hand, could provide a method for preventing the disorder as a whole. By manipulating the genotype of the very early embryo, development of the disorder could be prevented. However, public opinion is divided on this subject and many concerns about ethics are raised. The promise of raising healthy children is extremely tempting, but what will gene editing do to their progeny? Genome editing also gives rise to new forms of social inequality between high-income and low-income countries, but also to discrimination (designer babies). A call for a moratorium on human genome editing was heard from multiple scientists in Nature and Science who find this technique irresponsible (CGS). At an international congress in Washington in December 2015 scientists rejected the moratorium, but it was concluded that edited embryos will not be allowed to be born as of yet. More research is needed looking into safe methods for editing and in providing laws and control for when genetically enhanced children are eventually born (NRC, 2015).

If the differential susceptibility theory should be proven true for all genes involved in psychiatric disorders, it could be valuable to make better use out of the advantages these genes offer people living in a supporting environment (Dobbs, 2009). Then adaptation of the (social) environment to genotype could give an even higher advantage than manipulating the genome.

Ultimate implications: Evolutionary consequences of g x se interactions

Understanding the function of a trait could help to pinpoint how and why psychiatric disorders came to be. This knowledge can be incorporated in interventions or treatments of the disorder.

The DRD4-7R polymorphism, for example, is present in higher proportions in populations that historically migrated far away, compared to populations that remained close to their origins. It is hypothesized that natural selection could have favoured carriers of the 7 repeat in migrating populations. The 7 repeat is implicated in hyperactive, risk-taking and novelty seeking behaviour. These traits could be very adaptive in migrating populations because that is exactly how they would find new resources and be sensitive to novel stimuli, in order to survive (Chen et al., 1999). Jensen *et al.* (1997) too argue that in order for ADHD to be as highly prevalent as it is in the current society there should have been advantages to characteristics of ADHD that have been selected for. Also they broach the subject of differences between modern day society and the ancestral environment. In the last 10,000 years our culture and society has changed rapidly. It could be that our genome lags behind in evolution to this pace of environment. The characteristics of ADHD that could be meaningful to survival in the past could now mismatch the characteristics needed in our society, like focussed attention, long term planning and low motor activity. Assuming this theory is true, adaptation of environment to better fit the characteristics for people with ADHD could be a solution. In addition, knowing about this mismatch, teaching the children with ADHD and their parents about their limitations in one setting and their advantages in another (i.e. self-awareness) could help them get the best out of themselves without setting unreachable goals (and subsequently a lowered self-esteem). The clinical implication of this knowledge even extends to the administration of medication for ADHD, meaning that someone with ADHD could benefit from medication in one context (school) but could be worse off in another context (after school). A child that is sedated by medication doesn't play as much with other children and this will in turn affect his/hers social development and could subsequently worsen the symptoms of ADHD. This fails to achieve the very goal of the medication.

As is shown by this thesis, the behaviour of people may be influenced by genetic and environmental factors. The behaviour of others can subsequently affect our own behaviour. These effects are called 'indirect genetic effects' (IGEs) and they give evidence for a (social) environment that is heritable. This heritable environment is indirectly subject to selection and evolution (Wolf et al., 1998). IGEs add an extra dimension to GxSE interactions and have big implications for treatment. A trait can influence the expression of that

same trait in relatives or a partner. This can lead to positively synergistic IGEs. Small alterations in the genes involved with this trait can therefore result in large changes in expression of that trait (Wolf et al., 1998). Unknowingly, we already incorporate this knowledge into, for example, the parent intervention training. Getting a better understanding of these effects could be of great help in the development of prevention and treatments.

Conclusion

GxSE interactions play an important role in the development and treatment of psychiatric disorders. For almost all genes mentioned in this paper evidence for the differential susceptibility theory is found. This means that children carrying a 'risk gene' have an increased risk of developing a psychiatric disorder in an adverse environment, but, most interestingly, a decreased risk in a supportive environment. Therefore risk genes are better called plasticity genes. This knowledge provides a new way of treatment: personalized medicine. What works for one, doesn't have to be good for the other. I recommend investigating g x se interactions with an emphasis on social environment and its evolution, giving insight into the proximate and ultimate causes of this interaction in order to develop better prevention and curation methods, rather than studying them in an isolated fashion. Lastly, I want to stress the importance of focussing on the possibility that adaptation of the (social) environment to the genotype could give an even higher advantage than manipulating the genome or administrating drugs.

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