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The Interplay Between Genes and the Environment in the Onset of Obsessive Compulsive Disorder

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Introduction:

One of the greatest contributors to non-fatal health problems around the world is Obsessive Compulsive Disorder (OCD).[1] OCD takes a toll on many people as well as their close friends and families. It is not clear why one group of people might develop OCD while others, who are exposed to the same pressures, do not. Therefore, many researchers have investigated the etiological factors, origins, and backgrounds of OCD; rather than turning to reductionism or the obsolete argument of nature vs. nurture, scientists have turned their focus to the gene-environment interaction argument.

In the early 1900s, researchers started to acknowledge the role of genetics in the onset of OCD or what was previously known as "Obsessive Neurosis."[2] However, research has recently emphasized the importance of the environment in the onset of OCD.[3] Neuro-psychopathology raises the question of whether a genetically predisposed individual can be treated with medications targeting the neurochemical imbalances caused by these genes. Genetic profiling is often used when prescribing medications to OCD patients, emphasizing the importance of the epigenetic argument and the role of genetics.[4]

Recently, certain aspects within the field of neuro-psychopathology demand a further breakdown of the etiology of OCD, allowing the formation of neurobiological profiles for patients with OCD and creating a basis to predict the onset of OCD.[5] This topic was selected specifically because of its effect on modern-day medicine in the interest of grasping whether or

not OCD results from an unchangeable predisposition. This is an innovative perspective, beyond the effect of genetics on human conditions, because it questions how gene expression is impacted by experiences and interactions.[6]

In order to investigate this topic, specific terms need to be defined. Epigenetics refers to how environmental factors impact gene expression.[5] According to ASA, Obsessive Compulsive Disorder is a neuropsychiatric disorder in which people have obsessions (unwanted and recurring thoughts, sensations, or ideas) that push them to have compulsions (repetitive activities).[7] The Brain Derived Neurotrophic Factor (BDNF) gene signals the production of the BDNF protein, which regulates synaptic plasticity, differentiation, morphology, and neurodevelopment in the brain.[8] This gene has polymorphisms, which are associated with OCD amongst individuals who have experienced childhood trauma.[9] Furthermore, the personality trait harm avoidance, is identified with exorbitant fatigability, shyness, and uncertainty and has a 42-57% chance of being inherited.[10] The DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) is an American classification system of mental disorders created by the APA in 1995.[11] Finally, etiology refers to the cognitive, sociocultural, and biological factors that may play a role in the onset of a disorder.

Therefore, this essay will examine evidence upholding the gene-environment interaction argument by looking at the BDNF gene, the diathesis-stress model, genetic loading and parental OCD status, and concordance rates between twins. This is achieved by exploring studies by Hemmings et al, Bey et al, Wilcox et al, Hudziak et al and Van Grootheest et al, all of which contend that epigenetics presents an essential role in the onset of OCD.[9,10, 18, 21, 22] In addition, this essay will include the counterargument of the fundamental gene-gene interplay to answer the question: “To what extent does the interaction between genes and the environment contribute to the onset of Obsessive Compulsive Disorder?”

Evaluation of Evidence:

Gene-Environment Interplay

While it may be true that people develop OCD as a result of their upbringing, it is necessary to consider the role of genetics. Genetic marks may be intergenerationally transmitted and embody in OCD epidemics. Epigenetics does not refer to the changes in the fundamental genetic sequence; instead, it refers to the environmental factors that may activate and express certain genes.[12] As the neuro-epigenetics professor, Isabelle Mansuy, once said: "The genetic code, the hardware, is useless without epigenetic factors," implying that genes are the hardware while epigenetics are the software.[13]

The idea that OCD is inherited has been contested for a long time. Traumatic experiences at the time of maximal sensitivity, such as the phases of adolescence, may form long-term epigenetic factors, modifying the processes of maturation and neural circuits, hence prompting the onset of OCD.[14] Therefore, environmental factors do interact with genes to form OCD predispositions that carry social implications.[5]

Variations of the BDNF gene are known as alleles; BDNF-Val and BDNF-Met represent high and low activity of the BDNF system, respectively. BDNF-Met individuals are hypersensitive and more affected by adverse environments, leading to the onset of OCD.[15]

In 2010, Da Rocha et al found a positive association between the BDNF Met allele and OCD.[16] They also found that the Met allele induces early onset of OCD in males.[16] Furthermore, a sufficiently designed meta-analysis in ten studies involving a total of 2306 OCD cases and 4968 healthy controls showed that the BDNF Met allele was significantly associated with OCD in Caucasians ($p<0.05$), yet this association appeared to be insignificant in Asians.[17] Although both of these studies are subject to publication bias, they provide significant implications in the relationship between the BDNF Met allele, OCD, ethnicities and gender, begging for further exploration of the topic.

Hemmings et al carried out a study on a sample of 322 South-African Caucasians, 134 with OCD and 188 without to serve as the controls.[9] They investigated the interplay between OCD and adverse childhood experiences and the way in which this association is impacted by

the BDNF-Met allele. Subjects filled out the Childhood Trauma Questionnaire (CTQ) to determine physical and emotional neglect/abuse they may have experienced. They were to rate each situation based on occurrence from 1 (never) to 5 (very often). The study found that carriers of the BDNF Met allele who experienced emotional abuse were 35-61% more likely to develop OCD than BDNF-Val carriers. These findings reinforce the notion that neither the environment nor the BDNF Met allele alone predicts the onset of OCD, but simply the presence of the two factors in interaction allows the manifestation of OCD tendencies.[9]

One important limitation of this study is the low cross-cultural validity as it only included African Caucasians. This raises the question as to how replicable the findings are in distinct cultures. Recently, research has shown population dissimilarities in the BDNF gene where the prevalence of the polymorphisms varies across cultures, a fascinating aspect to consider.[15] One commendable aspect of the study is the ethical considerations taken into account, such as informed consent, which strengthened its reliability because it allowed participants to be aware of the nature of the investigation, which is important in genetic research. Furthermore, the study utilized method triangulation which heightened the validity of the results as numerous elements were taken into account. Overall, this study highlights the fact that a singular genetic marker cannot induce OCD on its own but requires to interact with an environmental stimulus.

Moreover, the gene-environment interaction can be clarified by the diathesis-stress model, a paradigm in psychology that theorizes that gene expression is controlled by the environment. Accordingly, the interplay between external stressors and genetic predisposition heightens the possibility of gene activation or expression, an intricate process needed for OCD to evolve. This can also be applied in the purview of psychopathology. The most primordial research investigating adverse experiences and behavior indicated that BDNF-Met individuals had a higher chance of developing OCD compared to BDNF-Val individuals. When childhood trauma was not reported, the two groups similarly exhibited no symptoms of OCD. Yet when childhood trauma was reported, BDNF-Met individuals showed remarkably more severe symptoms of OCD.[9]

Bey et al conducted a family study investigating a German cohort of 169 OCD patients and 57 of their non-OCD first-degree relatives utilizing retrospective data.[10] They aimed to investigate the interaction between childhood experiences, genetic makeup, and harm-avoidance and how it affects the onset of OCD. Each of the 169 OCD patients was matched with 157 non-OCD individuals based on age and gender. All participants were examined for asperity of early traumatic experiences through the Childhood Trauma Questionnaire, while harm avoidance was examined through the Temperament and Character Inventory. Even though the study found that OCD patients and their unaffected first-degree relatives had similar levels of harm avoidance, increased severity of early traumatic experiences was only seen in patients with OCD. The results of the study reinforce the paradigm of a diathesis-stress model where harm avoidance serves as the fundamental genetic vulnerability factor, and its interaction with early traumatic experiences induces the onset of OCD ($p=0.021$).

An imperative limitation lies in the matter that the sample was gender-biased, in which the cohort mainly consisted of females, reducing its representational generalizability to males. Furthermore, the study had low cross-cultural validity, posing a question of how applicable the results are to cultures other than German. Another one of the study's primary limitations is that the findings relied on retrospective data, which could have posed response biases that would have undermined the validity of the findings. Despite its limitations, this study surely formed an interactionist approach to explaining the groundings of OCD as it corresponds with the diathesis-stress model. This approach has proven useful in gaining an integrated understanding of the aetiology of OCD. Furthermore, the study is a family study. It can thus be suggested that the genetic tie formed between patients and their first-degree relatives sufficiently provides a correlation between heritability and the environment. Generally, these results imply that genetic predisposition may interact with external stressors to promote the onset of OCD.[10]

Central to the argument is epigenetics, where the interaction between genetic makeup and the environment is arguably always effective. Genes are the fundamental blueprint that affects maturational processes by creating neural networks across the brain. The environment then modifies those networks to reinforce a few while allowing the rest to deteriorate. Ostensibly,

having a high parental OCD status (at least one parent has OCD) may serve as an environmental stimulus. Parents with OCD are more likely to involve their children in compulsive rituals and project their obsessions onto their offspring. Since the offspring are already genetically predisposed to OCD, this may contribute to their OCD.

Wilcox et al conducted a retrospective family study on 1200 adults from 465 families in the USA.[18] They investigated the association between OCD among offspring and three parenting factors (control, overprotection, paternal and maternal care) taken from the Parental Bonding Instrument (PBI). Findings showed that those diagnosed with OCD were more likely to report parental overprotection and less likely to report parental care than non-OCD individuals. This association was more robust in those from multiplex families (more than one case of OCD) with a higher parental OCD status compared to those from sporadic families (only one case of OCD) with a lower parental OCD status. This is because offspring in multiplex families have a higher genetic loading and are more likely to be predisposed. This, together with having a higher parental OCD status, they are more likely to be brought up by overprotective and over-controlling parents. This, in turn, is more likely to induce an inter-generational transfer. It can thus be suggested that a higher parental OCD status and genetic loading can act as environmental stimuli for epigenetic profiles to emerge in offspring who are already genetically predisposed to OCD. In general, therefore, it seems that the interaction between environmental stimuli and genes plays a role in the manifestation of OCD.

The study is limited because it relied on retrospective data while the average age of participants in the cohort was forty-four; therefore, its validity could have been deteriorated by recall biases. A further limitation is that it was unknown how homogenous this sample was, as information was not provided regarding the participants' ethnicity. Therefore, it was impossible to see the role of cultural identity in the onset of OCD. Notwithstanding these limitations, the study utilized data triangulation compromising media advertisements, self-help groups, and treatment settings which guaranteed credibility.[18] Also, the findings apply to distinct fields of research like MDD, according to results from Fendrich et al.[19]

Additional exploration is needed to justify the epigenetic effects of high genetic loading and parental OCD status on the onset of OCD in offspring. Nonetheless, the insights gained from the available empirical evidence may help us prevent OCD among offspring.[20] For example, efforts could be made towards modifying the rearing behavior of parents.

Similar to family studies, twin studies are crucial in research regarding the aetiology of OCD. Monozygotic twins (MZ) share their entire DNA, and dizygotic twins (DZ) share only half, underlining the prominence of twin studies to exhibit distinct degrees of genetic inheritance utilizing concordance rates. These greatly substantiate the argument of epigenetics as they examine the environmental and genetic components affecting the exhibition of behavior. Twin studies demonstrate that multiple phenotypes could emerge from indistinguishable genotypes due to epigenetic factors.[21]

In 2004, Hudziak et al performed a twin study in the USA and the Netherlands investigating over 10,100 pairs of twins between the ages of eight to twelve to identify OCD tendencies in DZ and MZ twins.[22] For testing purposes, a CBCL-OCS (Child Behavior Checklist Obsessive-Compulsive Scale) questionnaire was filled out by the participants' parents to compare between subjects, allowing for the appraisal of the prevalence and sensitivity to OCD. The questionnaire considered multiple factors, including worries and strange behaviors. The concordance rates were an average of 55.5% and 51.8% for male and female MZ twins, respectively. In contrast, the concordance rates were an average of 34.5% and 23.25% for male and female DZ twins, respectively. The evidence from this study suggests that OCD is partially inherited and that the rest of the concordance rates are accounted for by non-shared environmental factors.[22]

In the same vein, Van Grootheest et al carried out a twin study to investigate the environmental and genetic factors that are involved in the onset of OCD.[21] The sample consisted of nearly 2800 MZ and DZ twin pairs from the Netherlands at the ages of twelve, fourteen and sixteen. Numerous measures were adopted to examine their obsessive-compulsive behaviors such as utilizing questionnaires that rely on self-reported data. Findings indicated that male and

female MZ twins had an average concordance rate of 50.6% and 54.3%, respectively, while male and female DZ twins had an average concordance rate of 28.3% and 32.7%, respectively.[21]

The scope of both studies were limited in terms of relying on subjective self-reported data, which is open to demand characteristics and is not an official form of diagnosis. Nonetheless, both studies used large sample sizes, which heightened the external validity of the findings and made them more reliable. Also, zygosity was identified through blood testing, which ensured that the MZ twins were in fact, identical.

One unanticipated finding was the gender differences within twins in both studies. It is possible, therefore, that gender plays a role in the manifestation of OCD. The dissimilarities between DZ and MZ concordance rates for developing OCD may be explained by the fact that MZ twins are usually brought up in similar environments and share the same genetic makeup; hence any differences point to non-shared environmental factors.[22, 21] Therefore, both studies add to the growing body of research that indicates that OCD results from the interplay between environmental factors and genetics, as seen by the concordance rates.

To conclude, the findings from the presented studies make several contributions to the current literature. First, OCD is a miscellaneous disorder where gene expression is more probable when exposed to a particular environment. Second, humans are intricate and controlled by more than just individual genes or the environment.

Gene-Gene Interplay

Even though there is strong evidence to assist the gene-environment interaction argument in the onset of OCD, some believe it is reductionist. Research shows the role of emotional regulation and the brain in the onset of OCD, highlighting the neurobiological facet and the inability to separate multiple biological variables. Additional research contends that the disorder can stem from the interaction of the genes with each other.[23]

Evidence has linked the enzyme-producing genes, COMT and MAO-B, associated with neurological functioning in the serotonergic and dopaminergic systems to a heightened risk of OCD. The rs362204 variant on the COMT gene has an impact that is reinforced alongside both variants, rs1799836, and rs6651806, on the MAO-B gene. It has been argued that OCD is associated with this fundamental gene-gene interaction.

McGregor et al conducted a study in 2016 aiming to investigate the interplay of genetic factors and how that affects the development of OCD.[24] The participant sample consisted of 52 OCD subjects and 195 non-OCD subjects who represented the control group. DNA of each participant was genotyped for the COMT and MAO-B genes. Participants were then asked through the SCID-I/P interview of any repetitive behaviors or persistent thoughts that they might have acquired in the last few years. A notable interaction between polymorphisms in the COMT and MAO-B genes was found in the case of OCD. This research provides insights into how the presence of the genetic variant on the COMT gene effects that of the variants on the MAO-B gene. The preeminent theoretical significance of this research is that the interplay between serotonergic and dopaminergic genes plays a role in the onset of OCD.[24]

The fact that ten polymorphisms were studied to identify potential links with OCD strengthens the validity of the study. However, the sample size is small; therefore, it may not be representative of the general population. Furthermore, the study did not consider variables such as race and age, thus evoking further concerns within the data's comparability and generalizability. While the study has gone some way towards enhancing our understanding of the gene-gene interaction in the onset of OCD, itis a pioneering one, suggesting that there are no systemic replications of it, and its reliability has not yet been endorsed.

Comparing the findings with those of other studies confirms the holistic interplay of the genes regulating the glutamatergic, dopaminergic, and serotonergic systems alongside environmental factors in the manifestation of OCD.[5]

It is crucial to acknowledge that the gene-gene contention in inducing OCD is still new and not well established. Therefore, further research needs to examine more closely the links between genes in manifesting OCD and whether some genes possess a more significant role than others.

Discussion:

A methodological evaluation is essential in answering the chosen research question after examining a myriad of studies of gene-gene and gene-environment interplays.

First, research involving family studies has been challenged due to the interrelatedness of nurture and nature. In a family, offspring experience the rearing environment and the impact of their parents' genotype, making it burdensome to assign a behavior to either the environment or genes. This could be considered both a weakness and a strength as not being able to isolate variables could further substantiate the argument of epigenetics and highlight the significance of their overlap. However, it is difficult to replicate the results of family studies as they are often exclusive to the families in question as in Bey et al.[10]

Moreover, when considering the methodological evaluation of twin studies, its reliability is substantiated by the large cohort size as it helps identify the commonality of the gene and behavioral patterns. Concordance rates are largely reliable as MZ twins share the same genotype; hence, any dissimilarity in behavior is probably because of environmental factors. Additionally, this methodology is easily replicable and has high internal validity. On the other hand, twin studies have low representational generalizability, and population validity as twins are not representative of non-twins. This is because twins have a specific genetic code, and we do not know yet if non-twins have the same code. Furthermore, there is no systemic evidence of reared apart OCD twins. Twins often experience substantially akin environments, posing a question of the effect of environmental factors on the onset of OCD.

It is crucial to point out that many of the studies presented here utilized the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) to understand the participants'

conditions. The researchers worked with experienced clinicians, allowing the interviewees' responses to be cross-referenced and carefully checked for credibility.[10, 9, 24] This lowered the risk of interviewer bias and allowed for a more reliable establishment of a link between heritability and environmental factors in the onset of OCD. However, there are various limitations to this diagnosis. One limitation is that the method enforces an etic approach to the investigation as it eliminates participants from the cohort who possess a form of OCD that does not fit the Western diagnostic criteria.[11] Additionally, the diagnostic process might make a client feel uncomfortable, which might induce "reactivity" in which the participant exhibits distress or other "OCD behaviors" that the clinician might then associate with the disorder.[25] Next, self-reported data is open to social desirability bias and the peak-end rule where obsessive and compulsive behavior could be under-reported or over-reported. In order to avoid this, the information could be obtained from medical registers.

Together, these studies support the notion of the epigenetics argument. Some researchers have presented sufficient evidence of the interchangeability of the environment and heritability by using family and twin studies. Others have highlighted the relevance of the DSM-IV (SCID-I) interview in providing a standardized way of comparing the participants' responses. However, the data obtained from the literature may be somewhat limited by ethnocentric bias. This is because all studies reviewed here dealt with individualistic cultures; therefore, their findings cannot be extrapolated to collectivist cultures. Also, since disorders are extremely intricate, OCD can be the product of various factors. Hence, it is reductionist to appoint a specific environmental stimulus or an "OCD gene." Therefore, it can be assumed that multiple genes interact with various environmental factors and social experiences to lead to the onset of OCD.

Conclusion:

These studies support the notion that OCD is a multifaceted disorder with underlying epigenetic roots. Consistent with the literature, the presented empirical evidence found that genetic markers may help explain the aetiology of OCD, and mitigating specific environments may lessen the risk of developing OCD.[18]

The prospect of epigenetics has significant implications for our grasp of how human behavior is affected by alterations in the fundamental genetic sequence due to environmental stimuli. Together, genetic and environmental factors represent how biological systems operate and advance; hence, if they were to be altered, then psychological factors crucial to human behavior will be altered as well.[5]

With respect to the research question: "To what extent does the interaction between genes and the environment contribute to the onset of Obsessive Compulsive Disorder?" The myriad of evidence reviewed here seems to support the idea that their interaction has a pertinent role in the manifestation of OCD. However, we cannot be completely confident with the answer due to the conflicting data encompassing it, particularly concerning the gene-gene interaction. In addition, the majority of the studies presented were limited in terms of culture, ethics, methodology, and generalization.

It is imperative to consider the potential ethnocentric bias in these findings. More information on self-sufficiency and extended family support in individualistic cultures on gene expression would help us establish a greater degree of accuracy. Moreover, several reports have suggested that an "enriched environment therapy" could reverse epigenetic marks.[14] There is, then, no doubt that further research is required in this field.

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