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Review Article

Gene environment interaction in the determination of human intelligence and behavior

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Abstract *The existence of individual differences in intelligence is a prominent aspect of human psychology, and it is well known that they can influence important life outcomes. The origin of individual differences in intelligence has been largely debated, and one of the biggest question is whether it is due to genetics or environment, commonly referred as the "nature vs nurture" debate. A large series of data collected in the last years have demonstrated that variability in cognitive abilities among different individuals are due to the interaction of genetic and environmental factors: genetics account for about 50% of difference among individual, while shared and non-shared environment account for 25% and 20%, respectively, the latter 5% being represented by errors in the evaluation of the cognitive abilities. Data on animal models have demonstrated that environment is able to modify genetically determined cognitive abilities, and that enriched environment can improve the performance of obtuse rats, even in presence of genetic abnormalities. However, the role played by genetics and environment does not remain the same during the entire lifetime. In fact, it has been demonstrated that the genetic component of human intelligence increase with age. This is due the genetically determined mechanism of neuronal repair, whose role becomes crucial with aging, but also by the reduction of the shared environment. The most recent models of gene-environment interaction in the determination of human intelligence postulate that at each age specific genetic and environmental influences occurs, producing a variability of IQ even within the same individual. Further evidence for the gene-environment interaction comes from the study of the psychiatric diseases, and in particular by the specific endophenotypes. These are biological markers of diseases such schizophrenia or mood disorders, which are genetically determined and are transmitted in a mendelian manner. These endophenotypes do not directly induce the disease, but represent the individual susceptibility to the disease. These susceptibility will produce a disease only in presence of environmental factors. Taken together, all these data demonstrate that the "nature vs nurture" debate is no more useful. Nature and nurture works together in the determination of human intelligence, and among environmental factor a crucial role in human is played by culture.*

Key words: Nature, nurture, endophenotypes, gene environment interaction.

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INTRODUCTION The existence of individual differences in intelligence and behavior represents not only a major topic of human psychology, but also a main feature in the life of common people. In the majority of case, such differences can influence important life outcomes, playing a crucial role in the development of social abilities and occupational success. The origin of individual differences in intelligence and behavior has been largely debated, and the main

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historical question about human intelligence is related to the role played by genes and environment, commonly referred as the "nature vs nurture" debate. A milestone in this debate is represented by the papers published by Francis Galton (1865) on the hereditary transmission of high intelligence and other abilities, suggesting that high abilities are substantively natural in origin, and transmitted via heredity from one generation to another. Remarkably, Galton's hypothesis was published one year before the publication of Mendel's classic paper on the laws of heredity. Unfortunately, the degeneration of the "nature vs nurture" debate has represented the source of dramatic events in the life of millions people. From an historical perspective, both the theory of a strictly genetic origin of human behavior and the hypothesis of a predominant role played by environment have been used to support the ideological basis of bloody dictatorships in the XX century. In Germany, the rediscovery of Mendel's work at the beginning of the 20th century was used to emphasize the inheritance of a number of so called "undesirable traits", such as mental retardation, mental illness, criminality, drunkenness, prostitution, and poverty (Garver & Garver, 1991). As a consequence, the Nazi ideology of Adolf Hitler, entirely based on the theory of a genetic origin of human behavior, produced the Nazi eugenics movement, characterized by a program moving from the suppression of children born with birth defects to the extermination of other "undesirable elements" such as Jews, Gypsies, mental patients (Garver & Garver, 1991). The ultimate aim of the Nazi eugenics movement was to demonstrate the existence of a "Jewish race" whose negative attitudes were genetically determined and, thus, not preventable even in children. On the other hand, the Soviet ideology of Joseph Stalin was largely driven by the idea that human characteristic are determined only by environmental factors, and that no rules can predict the transmission of human characteristic by reproduction. In 1948, genetics was officially declared "a bourgeois pseudoscience", and all genetic research was discontinued.

The lack of scientific basis for both the naturalistic and the environmentalist theories has been demonstrated by a large series of data collected in the last decades. In fact, it has been clearly demonstrated that variability in cognitive abilities and behavior among people are due to the interaction of genetic and environmental factors. Useful information in this field are provided by the study of monozygotic (MZ) and dizygotic (DZ) twins. MZ twins show 100% homology in their DNA, being derived by the fusion of a single sperm with a single oocyte. Generally, MZ twins also share the environment in which they spent childhood, since they grow up in the same family, attend the same schools and likely have common friends. On the other hand, DZ twins have only 25-50% similarity in their DNA, being derived from the fusion of two sperms with two eggs. However, like MZ, also DZ twins generally share the environment in their childhood. If we look at the concordance rate between a couple of twins in their cognitive abilities or in their behavior traits, an increase in the concordance between MZ twins as compared to DZ twins will indicate the presence of genetic factor underlying the investigated phenotype. Several studies have been reported in this field. Nichols (1978) evidenced that MZ and DZ correlations for cognitive total score were 0.86 and 0.62, respectively, and for five special abilities were 0.74 and 0.52, respectively, leading to a measurement of the broad heritability of general intelligence at about 0.7 (Deary *et al*, 2006). Based on these results, it has been possible to calculate that genetics accounts for about 50% of difference among individual (Deary *et al*, 2006), while shared and non-shared environments account for 25% and 20%, respectively, the latter 5% being represented by errors in the evaluation of the cognitive abilities. Since human intelligence and behavior are determined by the interaction between genes and environment, they can be considered as complex traits. In genetics, the study of the inheritance of specific phenotypes is based on the distinction between Mendelian traits and complex traits. Mendelian traits are qualitative (e.g. hair color or shape), entirely determined by genetic factors and inherited according to the Mendel's laws. On the other hand, complex traits are quantitative (e.g. height, weight), derive from the interaction of several genes with the environment and are not inherited according to the Mendel's

laws, although each single gene involved in the constitution of the genetic background of a complex trait is inherited in a Mendelian manner.

GENE-ENVIRONMENT INTERACTION

Age related differences

If the genetic model to apply to human intelligence and behavior is the multifactorial inheritance, a main questions must be addressed: how genes and environment can interact in order to determine the final phenotype? A first answer come from the observation that the heritable component of human intelligence does not remain identical during the lifetime. In fact, an increase in the heritability of cognitive abilities with age from about 30% in young childhood to as much as 80% in adulthood has been demonstrated (Spinath *et al*, 2006; Johnson *et al*, 2007; Jacobs *et al*, 2007; Edmonds *et al*, 2008; Deary *et al*, 2009). The most recent models of gene-environment interaction in the determination of human intelligence postulate that at each age specific genetic and environmental influences occurs, producing a variability of IQ even within the same individual (Brant *et al*, 2009). This is in part due to the genetic control on the morphological changes affecting brain during development, with the activation of different genes at different ages (Deary *et al*, 2009). However, in addition to the genetic contribution increase across development, also non-shared environment contributes greatly to change across ages, while shared environmental influences decrease, being very modest in adulthood as compared to early childhood (Brant *et al*, 2009). The non-shared environment includes all those variables that are unique to each individual, and these experiences during adulthood can be represented by several cultural and social factors. Thus, the personal choices, including reading, watching TV, hobbies, can be considered as non-shared environments playing an important role in the determination of cognitive abilities in adulthood.

Another mechanism which could be invoked in order to explain the variable heritability at different ages is related to neuronal repair. During brain aging, several environmental insults can produce a neuronal damage by inducing oxidative stress and inflammation. Neurons protection and repair play a crucial role in order to prevent neuronal damage. These defense and repair processes are genetically determined, and the presence of functional variants within genes involved in neuronal protection and repair likely induce age-related interindividual differences in cognitive phenotypes as a consequence of different levels of neuronal damage. This hypothesis is supported by the finding that variation in the gene for apolipoprotein E is associated with general cognitive ability at age 79 but not at age 11 years (Deary *et al*, 2002). Again, this is another example of gene-environment interaction: brain damage is caused by environmental agents, but neuronal protection and repair is genetically determined.

Animal models and the role of enriched environment in cognitive abilities

Another important source of information about the gene-environment interaction in the determination of intelligence and behavior is provided by experiment on animal models of genetic disease characterized by the presence of mental retardation. In fact, it has been demonstrated that environmental enrichment increasing the levels of sensory, cognitive and motor stimulation in housing conditions is able to induce a range of dramatic effects in cognitive abilities and behavior of animal with different kinds of brain disorder (Nithianantharajah & Hannan, 2006). It has been demonstrated that these effects are due to the environmental enrichment ability to induce modifications in brain structure and function, increasing the birth and maturation of new neurons into functional circuits, enhancing the expression of molecules involved in neuronal signaling, and promoting synaptic plasticity. Brain function and plasticity are influenced by these modifications via an effect on synaptic transmission, enhancing signaling between neuronal ensembles and strengthening neuronal circuits. In this way, the brain may more efficiently utilize existing

neuronal networks and recruit alternative networks when required (Nithianantharajah & Hannan, 2006).

Genes, environment and behavior: the molecular basis of human aggressiveness

It is now largely accepted that inheritance plays a significant role in the predisposition of humans to various behavioural disturbances, including antisocial and aggressive behaviour. Considerable evidence from twin and adoption studies indicates that both genetic and shared environmental factors play a substantial role in the liability to antisocial behaviour (Maes *et al*, 2007). A detailed evaluation and meta-analysis of 24 genetically informative studies concerning aggression concluded that heritability accounted overall for about 50% of the variance (Miles & Carey, 1997; Rhee & Waldman, 2002). At the same time, it must be stressed that there are no genes directly acting on behaviour, being the genetic influence on behaviour mediated by the activity of central regulators, such as neurotransmitters (Popova, 2008). The serotonergic, catecholaminergic and dopaminergic systems are all involved in the genetic activity on human behaviour. The serotonergic system has been implicated in the regulation of impulsivity and aggressive behaviour (Ferrari *et al*, 2005; Nelson & Trainor, 2007). In general, serotonergic hypofunction has been associated with increased impulsiveness and impulsive aggressive behaviour. The regulation of serotonergic system might be related to genetic variability, and several studies have been focused on understanding the functional effects of specific polymorphisms within genes encoding for the key enzymes of serotonin synthesis, for the serotonin transporter (5-HTT) and for the serotonin receptors (Sugden *et al*, 2009; Wang *et al*, 2009 Sun *et al*, 2005; Chen *et al*, 2008). Several association studies relating the functional variant in the serotonin biosynthetic enzyme tryptophan hydroxylase (TPH; A779C substitution), the serotonin transporter (5-HTT, 5-HTTLPR allele), the 5-HT1B receptor (G861C, C129T substitution) and the 5-HT2A receptor (T102C) to the aggressive behaviour have been reported (Staner *et al*, 2002; D'Souza & Craig, 2008; Popova, 2006; Popova, 2008). Recently Naumenko *et al* (2009) concluded that 5-HTT is also involved in the regulation of genetically determined fear-induced aggression, being the expression of 5-HTT gene in the frontal cortex significantly reduced in rats selected for high aggression in comparison with non aggressive rats.

Also catecholaminergic systems are involved in the regulation of aggressive behaviour, in interaction with other neurobiological mechanisms. Also in this case, the gene-environment interaction play a key role. In fact, norepinephrine and dopamine lower the threshold for an aggressive response to environmental stimuli through the activity of two enzymes responsible for catecholamine catabolism in the brain: catechol-O-methyltransferase (COMT) and monoamine oxidase A (MAOA). Genes coding for these enzymes show common functional polymorphisms affecting their transcriptional activity. Concerning the COMT gene, great attention has been devoted to the functional SNP (Val158Met) in the coding region, with the Met substitution leading to approximately 40% reduction in enzyme activity by conferring thermolability (Hosák, 2007). Some authors have found a correlation of the Met allele with increased aggressiveness particularly for males and frequently associated with schizophrenia. McDermott *et al* (2009) demonstrated that aggression occurs with greater intensity and frequency as provocation is experimentally manipulated upwards, especially among low activity MAOA (MAOA-L) subjects.
In fact individuals carrying a particular polymorphism of MAOA gene (with lower enzymatic activity of the encoded protein), when exposed to critical environmental factors like maltreated in childhood, punitive parenting or abuse experience, exhibit aggressive impulsive and antisocial behavior and can become violent adult. Individuals who had both childhood maltreatment and mutant MAOA would be more likely to exhibit antisocial behavior than individuals who had childhood maltreatment but normal MAOA or no childhood maltreatment and mutant MAOA (Caspi *et al*, 2002). The first evidence of a human mutation in the MAO gene associated with aggressive behaviour came from a study by Brunner and colleagues (1993). This study was

conducted on a large Dutch family in which several of the males had undesirable behavior like impulsive aggression, and rape. Among males with the low MAOA activity genotype, antisocial scores were higher in those maltreated in childhood than in those not maltreated. By contrast, among males with high MAOA activity, there was no excess of antisocial behavior in relation to child abuse. T. Moffitt (Caspi & Moffitt, 2006) claims that the low MAOA activity genotype is a vulnerability factor which, together with an environmental factor, predisposes to violent behavior; beside the high MAOA activity genotype play a protective role against environmental insults. According to another research (Beaver *et al*, 2008) males with this polymorphism are twice as likely to join a gang, moreover gang members with these mutations are far more likely to use a weapon than other members. Given numerous evidences we can sustain the strong role of gene-environment interaction, thus the studies of MAOA activity in associated with critical environmental factors is a good element to predict aggressive and anti social behavior.

Lessons from psychiatric disease: the endophenotypes

New insights in the study of the gene-environment interaction in the determination of human behavior comes from the dissection of the psychiatric diseases, aimed to identification of more discretely inherited neurobehavioral subcomponents representing intermediate phenotypes, or "endophenotypes" (Gottesman & Gould, 2003; Cannon & Keller, 2006). Endophenotypes are biological markers linking sequence variations within specific genes to specific neural system dysfunctions representing the molecular basis of the genetic liability to mental diseases such schizophrenia or mood disorders.

Cannon and Keller (2006) proposed six properties for the characterization of endophenotypes:

1. Endophenotypes should be heritable;
2. Endophenotypes should be associated with causes rather than effects of disorders;
3. Numerous endophenotypes should affect a given complex disorder;
4. Endophenotypes should vary continuously in the general population;
5. Endophenotypes should optimally be measured across several levels of analysis;
6. Endophenotypes that affect multiple disorders should be found for genetically related disorders.

These properties clearly indicate the meaning of the role played by endophenotypes in the pathogenesis of mental diseases. Endophenotypes are genetically determined, being associated to specific gene variants, and are transmitted in a mendelian manner. They do not directly cause the disease, being detectable also in the general population although with a lower prevalence than in affected individuals, but represent the individual susceptibility to the disease. Each disease is characterized by the presence of several endophenotypes, some of which are specific for the disease while others are common for multiple disorders. The overall presence of a number of endophenotypes determine the global genetic and biological liability to mental disorder: however, these liability will produce a disease only in presence of environmental factors.

A clear example of endophenotype comes from the study of the P_{50} sensory gating ratios in patients with schizophrenia as compared to normal people (Patterson *et al*, 2008). In fact, it has been postulated that the sensory gating problem observed in schizophrenia may result from neuronal hyperexcitability derived from a defect in sub-cortical and cortical neuronal inhibitory pathways. An useful approach for the assessment of these inhibitory mechanisms is represented by auditory dual-click or conditioning–testing task, based on the presentation of paired clicks separated by an interval of 500 ms, and a positive-polarity brain response occurring approximately 50 ms poststimulus measured by the P_{50} wave of the average auditory evoked brain potential. Several studies have reported that in healthy control subjects the P_{50} gating ratio is smaller than in patients with schizophrenia, indicating more effective sensory gating. P_{50} auditory evoked potential sensory gating deficit has been associated to single nucleotide allelic variants in the promoter region of alpha-7 acetylcholine nicotinic receptor gene (CHRNA7), thus providing

evidence for a genetic variant responsible for the liability to schizophrenia (Martin *et al*, 2007). Another example is provided by the relationship between the short allele of the 5 HTT gene and depression. In fact, it has been showed that carriers of this allele have increased anxiety-related temperamental traits, increased amygdala reactivity to stressors and elevated risk of depression (Canli & Lesch, 2007). Again, also in this case we have the example of a specific genetic variant inducing a biological condition increasing the risk for a disease but only as a reaction to specific environmental agents, represented in this case by stressors.

One of the most interesting model of gene environment interaction is represented by Anorexia Nervosa (AN), a psychiatric disorder characterized by the fear of gaining weight leading to a strong drive to become thin, lower than normal body weight, and a distorted body image (Bulik *et a*l, 2007). For decades AN was considered a disorder influenced primarily by family and sociocultural factors; however family and twin studies have consistently demonstrated that AN is strongly familial and that familiarity is due primarily to genetic factors affecting serotonergic, dopaminergic and leptinergic systems. Nonetheless, environment may play an important role in the expression of underlying genetic predispositions (Bulik *et al*, 2005). In fact AN is present almost exclusively in Western industrialised nations, likely due to cultural factors, such as the promotion of thinness as the ideal female form. Moreover, a distorted self image due to psychological difficulties is often detect in AN patients. Thus, AN can be considered as the result of the interaction of at least three factors: genetic, social and psychological.

CONCLUSIONS Taken together, all the reported data demonstrate that the "nature vs nurture" debate does no more make sense. Nature and nurture works together in the determination of human intelligence, behavior and mental diseases. The identification of genes involved in the inheritance of such traits will play a crucial role in understanding the biological basis of human intelligence and behavior. However, also the study of the environmental agents acting on the genetic background has an huge relevance. In fact, so far we cannot modify genetics factors, but we can modify environment, and these modifications can reinforce or weaken genetic susceptibility. Environment, in the study of human intelligence and behavior, is represented not only by the life style, but also by culture. Some disorder such as aggressiveness o anorexia nervosa can be considered as "cultural" diseases. This will probably represent one of the most important issue of debate in the next future.

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