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EPIGENESIS AS KEY CONCEPT FOR UNDERSTANDING FUNCTIONAL AND DYSFUNCTIONAL REACTIONS OF HUMAN BEINGS TO THEIR ENVIRONMENT

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SUMMARY

Epigenetics is regarded as a promising research field to better understand the interplay between genetic and environmental factors underlying both typical and atypical developmental processes (from embryonic cell specialization to severe neurological and mental disorders). The aim of this paper is to describe the history of the concept of epigenesis from its Aristotelian foundation. Emphasizing the relation between internal powers and external factors of change, Aristotle seems to anticipate the current meaning of epigenetics, coined by Conrad Waddington in 1940 and then developed by the modern genetics. The discovery of epigenetic mechanisms has challenged the static nature of DNA pointing out the dynamic and reversible changes occurring in response to environmental prompts. This stimulates considerations on the relational nature of life in the response to various environmental stimuli.

Aristotle's concept of epigenesis

The main object of this intervention is the actual concept of epigenetics, a field of research that links together several sciences,

Key words: Epigenetics - Aristotle - GxE interaction - Schizophrenia

namely biology, genetics, psychiatry, and so on. In this light, epigenetics promises to develop an interdisciplinary field of research, unifying several perspective on the interaction between genetic inheritance and environmental factors.

In this first section, our attempt consists in reconnecting the contemporary usage of term "epigenetics" with its Aristotelian ancestor, that is *epigenesis*. I will argue that the ancient term is related to the modern one not only for its relevance in Aristotle's theory of generation, but as part of his broader paradigm of motion and change. Evidences for this hypothesis can be achieved in several works of Aristotle, belonging to ethics and rhetorics more than biology. In these context the term *epigenesis* identifies the apparition of a new feature in an already existent being, at the end of a gradual change. Change can be instantiated from external causes, simply suffered from inanimate, but actively receipt from living beings, whose life can be described as a continuous mediation of internal and external factors, not always crowned with success.

The Aristotelian term *epigenesis* has a really rich history - that often coincides with the fortune of *De generatione animalium* (GA). As a matter of fact the actual term "epigenetics" has been coined in 1940 by Conrad Waddington, with explicit reference to Aristotle[1]. But long before Waddington's usage of this term, a similar reference to Aristotle has been proposed, inside the debate about the process of generation of living things, beginning from 1550. In this context the term *epigenesis* has been opposed to preformationism[2]. For the advocates of this theory, all the parts of the *foetus* exist since the beginning of the generation process. In their opinion, this process is only a continuous growth of the already existent parts through the addition of material elements. A version of preformationism was already opposed by Aristotle in GA, where he suggests an alternative account, according to which male and female play, respectively, the role of the formal and the material cause of a progressive development of the parts, starting

from the hearts, which is the first principle of life[3]. Then, in this first stage of epigenetics modern history, the recovery of the Aristotelian term was intended to describe the gestation process as a progressive development of the body parts that, as such, are not given by parents.
The second, most relevant, stage of epigenetics is either more recent, and more related to the actual concept of epigenetics. In fact, as already mentioned, this term was coined in 1940 by Conrad Waddington, even before the discovery of DNA. But the attempt of Waddington is no more the polemic against the preformationism view, but rather the explanation of the "interaction between genes and their product". Then, the field of research of Waddington is very close to the actual epigenetics, even if several differences - technological as well as theoretical - separate them. As we illustrate in the second part of this intervention, what today epigenetics try to explain is not only the modification of the phenotype of the cells as response to inner *stimuli*, but also the modification - in term of activation or deactivation - of single branch of DNA as response to environmental solicitations and stresses. In my opinion, it is not the polemic about preformationism and *homunculus* theory, but the actual meaning of "epigenetics", and the special emphasis on the interaction between internal genetic predisposition and external factors of change that is mostly related to the evidences of term *epigenesis* in Aristotle's *corpus*[4].
Curiously, despite the large fortune of the reference to Aristotle, there are not many evidences of this term in the *corpus*, and only three occurrences can be found in GA. At the end of a brief analysis of the available occurrences, it may be possible suggest that *epigenesis* belongs to the Aristotle's wide theory of change and motion, more than biology and embryology.
First of all, if we examine the distribution of the term *epigenesis*, we first realize that it is used in various purposes works, from biology to rhetorics and ethics. The term is used only 3 times in GA, although not these but the occurrences inside HA refer to *epigenesis* as a biological term.

If we push the analysis to the context in which Aristotle uses the term, we find that the most frequent usage is with the meaning of "add" or "join". This is also the case of the only occurrence in the GA really relevant for the theme of generation:

> *Not only must the mass of material exist there from which the embryo is formed in the first instance, but further material must constantly be added that it may increase in size*[5].

From this point of view, the Aristotelian term *epigenesis* seems to be only weakly connected to the modern concept of epigenetics. The required material for the progressive growth of the individual seems to be mostly connected to the debate against *homunculus* theory, rather than to the reaction of the organism to environmental stimuli. However, a second family of occurrences is found in the *corpus*, in which the meaning of *epigenesis* is not strictly equivalent to "add" or "join". A good example can be found in NE:

> *Pleasure completes the activity not as the inherent state does, but as an end which supervenes as the bloom of youth does on those in the flower of their age. So long, then, as both the intelligible or sensible object and the discriminating or contemplative faculty are as they should be, the pleasure will be involved in the activity; for when both the passive and the active factor are unchanged and are related to each other in the same way, the same result naturally follows*[6].

The term is also used with the same meaning in Rhetoric, although not recognised in some translations:

> *Similarly an element of pleasure supervenes even in mourning and lamentation*[7].

In my opinion the frequent association of the term *epigenesis* with the theme of pleasure does not make it specific of the ethical reflection, but allows to highlight its meaning[8]. In the texts just quoted,

epigenesis is used to describe a qualitative change that comes at the end of a quantitative variation. In this sense, the movement which the term *epigenesis* refers to is close to *genesis*, as opposed to the various cases of *kinesis*[9]. From this point of view *epigenesis* is a sort of movement that ends up with an outcome not entirely reducible to the progressive, diachronic change that is still required. Unlike the complete cases of generation, the epigenetics phenomena happen to (supervene to) an already formed individual, which genus is not changed but instead fulfilled for this latest *metabole*[10]. Strictly dependent on its prerequisite, what supervenes is also irreducible to its *hule*, and in the case of the pleasure, it is ultimately something different from the diachronic *praxis* during which it appears.

This technical meaning of Aristotelian *epigenesis* is closely connected to modern epigenetics, especially for one reason. Either the ancient and the contemporary concepts emphasize not only the inner factors but also, and not secondarily, the premises of the epiphany of the pleasure that comes from external environment (*periechon*)[11].

As often observed, Aristotle's conception of life and living things can be regarded as an homeostatic process that continuously seeks for an equilibrium between external solicitations and internal tendencies[12]. The actuality (*entelecheia*) of life can be preserved only making the right use of the external factors of change, as long as the living subject is able to modify its response to the environment. Aristotle's emphasis on the relation between internal powers to change and external factors of change, more than the narrow use of the term *epigenesis*, can be regarded as a possible linkage to the modern concept of epigenetics.

The modern concept of epigenetics: from embryonic development to adult age

The equilibrium between external stimuli and internal reaction is easily observable in the microscopic world of biology in which

the cells, or all of they contain, are interdependent with their surrounding. The concept of epigenetics[13] has gradually taken on an increasing relevance in recent years for scientific research and it is constantly evolving in conjunction with related phenomena, widely studied and interpreted, thereby providing the definition that embodies contemporary usage of the word.

The genome is depositary of genetic information; the DNA is codified and inherited by daughter cells, and it is different from epigenome that represents the sum of all chromatin modifications in an organism. The epigenome interacts with the DNA and activates or suppresses the expression of genes. The epigenome is a part of surrounding DNA microenvironment and its interaction with it. The epigenome changes in response to intra-cellular signals, also coming from neighboring cells, or from the external world. Hence, epigenetics emphasizes the ecological nature of the cell as ecological niche. This is particularly clear considering the effect of epigenetic mechanisms on stem cells during embryonic development.

Stem cell niche refers to the biological microenvironment that interacts with stem cells to regulate cell fate. During embryonic development, various niche factors act on embryonic stem cells to alter gene expression, and induce their proliferation or differentiation for the fetus development. Cell fate depends on their interactions with neighboring cells. The physical structure of the niche varies between organisms and stem cell types, its composition ranging from a single cell or cell type to many cells of varying cell types. Individual stem cell niche also uses distinct combinations of signaling molecules to control stem cell proliferation and self-renewal. For some stem cell types, the activation of a single signaling pathway by the niche is sufficient for promoting stem cell self-renewal. However, in other cases, specific signals or combinations of signals are needed by different niches to control stem cell self-renewal, many of which appear to function as short-range signals. Examples of such signals are protein, hormones and chemical molecules[14,15].

As it is known, in the cellular nucleus there are the complexes of DNA and proteins called Chromatin. DNA is wrapped around the histones (H2A, H2B, H3 and H4) to form the nucleosome[16]. The pack of nucleosomes in a highly compacted form of 30nm chromatin fibers, plays a crucial role in the regulation of gene expression and other DNA-dependent activities[17]. Transcription factors bind not only to gene promoters, but also to other transcription factors and non-coding RNA in a complex network of genomic targets involved in a particular adaptive response. Chemical tags were attached to our genetic code, like a bookmarked pages of a book, signaling to our bodies which genes to ignore and which to use. For instance, DNA 5-Methyl Cytosine of the dinucleotide sequence CpG is related with gene silencing. The same function is performed by Methylation of 27 lysine of H3 Histone and by Methylation of 9 lysine of H3 Histone. By contrast, Methylation of 4- and 36- lysine of H3 Histone, and, histone acetylation are related to transcriptional activity. These are examples of epigenetic mechanisms that control chromatin organization to influence gene expression[18]. Other epigenetic mechanisms are known, such as phosphorylation, presence of histone variants and of non-coding RNA.

Chromatin structure and nucleosome modification can be inherited, in fact several epigenetic tags derive from parental chromosomes and remain during embryo formation; this persisting imprinting strictly depends on the continuous activity of enzymes that maintains the methylation marks of imprinted genes during cleavage. The reversibility of epigenetic processes explains the susceptibility of DNA to environmental factors and the related implications on the phenotype development, as demonstrated by different studies[19].

Homozygote twins provide an excellent source of information regarding the joined effect of genetic and environmental factors on phenotype. Indeed, identical twins share the same genes but the environment in wich they live in becomes increasingly different with

the advance of their age (when the non-shared environment becomes greater than the shared environment they joined as children). This unique aspect of twins makes them an excellent model for understanding how genes and environment contribute to certain traits, especially complex behaviors and diseases.

An important study examined the methylation profile of 80 pairs of monozygotic (namely, identical) twins at different ages. Researchers showed that monozygotic twins show different disease susceptibility, suggesting the possibility that epigenetic differences increase with ageing. Indeed, while young twins had similar amounts of DNA methylation, older twins considerably differ in the amounts and patterns of this modification[20].

The long-term pattern of epigenetically marked genes creates the epigenome that finally determines physical and behavioral phenotypic outcomes; chromatin configuration is considered to be a link between external environment and cellular DNA. Epigenetic processes are involved in normal development (e.g. cell differentiation) as well as in adaptive response to the environment and in pathological processes. Chemical pollutants, dietary components, temperature changes and other external stressors may, indeed, produce long-lasting effects on development, metabolism and health, sometimes even in subsequent generations. However, the underlying mechanisms remain largely unknown, particularly in humans.

The interplay between genetic and environmental risk factors in severe mental disorders

A promising application of epigenetic research is related to the aetiology of major psychiatric disorders, such as psychosis, in order to better understand the joined effect of genetic liability and environmental exposures. This seems particularly important since these syndromes - characterized by severe symptoms, chronic course, and significant impairment - are one of the major causes of the health

burden in the world and they absorb the greatest part of funding for mental health care[21].

Psychotic disorders are now regarded as complex and multi-factorial disease resulting from heritable and non-heritable factors, such as obstetric complications, poor maternal care and maltreatment, migration, drug use, and stressful life events. The first wave of genetic research on psychotic disorders was focused on identifying single genetic polymorphisms directly related to the pathogenesis of the disorder, affecting the dopaminergic brain system responsible of key psychotic symptoms, such as delusion and hallucination. However, this research line has become progressively disappointing given the large number of genes that were found to be associated with psychotic syndromes. Indeed, a recent collaborative study published in Nature in 2014 analysing the data of 37,000 patients with schizophrenia and 113,000 healthy controls found that as much as 108 loci (single-nucleotide polymorphisms, SNPs) were associated to the disease, by altering not only the dopamine transmission, but also the glutamate transmission (which regulates dopamine transmission), together with some neurodevelopmental process, immunity, and stress response[22].

Another proportion of risk is conveyed by copy number variants (CNVs), also involved in other neurodevelopmental diseases such as autism, epilepsy, and learning disability. However, large-scale genome-wide association studies showed that cumulative genetic scores, which account for a number of genetic loci, and copy number variants were able to explain only a limited proportion of the genetic liability for psychotic disorders. This suggest that the major part of risk is likely to be explained by gene-gene interactions (also called epistasis) and by gene-environment interaction[23,24].

According to the last perspective, it is possible that particular genes make individuals more vulnerable to specific risk factors, as in the case of the people carrying a particular variant of one of the

genes involved in dopamine transmission (COMT) that were found to be more at risk of developing psychotic symptoms after heavy marijuana use. Alternatively, the joint effected of environment and genetic risk factors might be explained by epigenetic modification, meaning by differences in gene expression driven by environmental exposures.

According to the current state of knowledge, recognized post-natal environmental risk factors for psychotic disorders include illicit drugs able to stimulate subcortical dopamine transmission, such as cocaine, amphetamine, or in cannabis. Other known risk factors are related to the effect of stress on the dopamine system and, therefore, on psychotic symptoms, via the alteration of the Hypothalamic-Pituitary-Adrenal Axis (HPA axis) that regulates stress-response behaviours. These includes, living in a highly urbanized area, being a member of a discriminated group (such as, ethnic or sexual minority group), being exposed to severe sexual or physical abuse in childhood, and, to a minor extent, to stressful life event in adulthood[25]. Accumulating evidence from both animal and human studies demonstrated that poor maternal care, early maltreatment, and social exclusion determine an overstimulation of the Hypothalamic-Pituitary-Adrenal Axis, which in turn may result in a long-term impairment of the HPA axis negative-feedback mechanisms. Eventually, this stable over-reactivity is associated with increased anxiety and reduced ability to cope with daily life stressors, producing long term changes of brain structure and functioning, such as altered level of basal and awakening cortisol, altered functioning of the amygdale and the prefrontal cortex, and reduced volume of the hippocampus[26]. Furthermore, basal cortisol levels correlated with subcortical dopamine levels[27] and are associated with the course of psychotic disease[28].

According to an integrated socio-developmental cognitive model of psychotic disorders[29], psychosocial risk factors interact with genetic

liability in stimulating the dopamine systems and, eventually, provoking psychotic symptoms, particularly persecutory delusions and hallucinations. These abnormal perception and thoughts determine increased level of anxiety, depression, and insomnia that, in turn, tend to fuel the dopamine system. For instance, there is preliminary evidence that social isolation in rats and early adversities in healthy volunteers are associated with an increased striatal dopaminergic response to subsequent social stressors and stimulant drugs[30]. In this way, a vicious cycle is established linking genetic liability, dopamine dysregulation, and psychosocial stress.

In this framework, epigenomic alterations might represent one of the mechanism underlying genes by environment interplay. Since the onset of psychotic disorders mainly occurs between the second and the fourth decades of life, and the impact of environmental risk factors is significantly related with their timing, epigenetic studies might elucidate how environmental risk factors (including social adversities) modify gene expression during developmental periods, inducing stable and potentially heritable changes[31,32]. Indeed, several studies demonstrated that poor maternal care in rats and early adversities in children[33,34] were related to hypermethylation of the promoter region of the gene encoding for glucocorticoid receptors (called NR3C1), which is involved in the negative feedback regulation of the HPA axis (the stress response system) and, indirectly, modulates the subcortical dopamine activity. Although most of the human studies were based on peripherally accessible cell types, such as blood or saliva cells, there are suggestions that these cells reasonable reflect differences in epigenetic profile of brain cells. Moreover, a well known post-mortem study of suicide completers, subsequently replicated, found that hippocampal cells of suicide victims who were abused as child had increased methylation of the NR3C1 genes and decreased levels of the corresponding RNA-messenger compared to non-abused suicide victims[35,36]. Besides glu-

cocorticoid receptors, the effect of psychosocial stress on the brain was related to epigenetic modification (mainly hypermethylation) of genes involved in cellular signaling systems, immune response, or neuroplasticity, such as FKPB5, AVP, and BDNF, although some studies did not replicated the findings[37].

Another promising research line investigated the association between epigenetic modifications and stressful experience occurred in adulthood. A study using the experience sampling method, which assess daily mood changes related to daily life events, found that both in severely depressed patient and healthy individuals the relationship between negative events of daily life and unpleasant affect (anxiety, irritability, sadness…) was modulated by a particular variant of a gene coding for DNA methylation; intriguingly, this moderation effect was not observed in the relation between positive events and pleasant emotions[38].

Conclusions

In light of these preliminary evidence, epigenetics seems to be a promising research field to better understand the interplay between genetic and environmental factors underlying both normal developmental processes (from embryonic cell specialization to ageing) as well as a number of severe, chronic, and impairing disorders (such as cancer, dementia, or psychotic disorders). Additionally, epigenetic mechanisms challenge the static nature of DNA pointing out the dynamic and reversible changes occurring in response to environmental prompts. The interaction between inner, static powers and dynamic factors of change can also turn on several philosophical and widely humanistic debates about the intrinsically relational nature of life.

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1. WADDINGTON C. H., *The Epigenotpye*. Endeavour 1942; 1: 18-20.
2. On this argument, see MAIENSCHEIN J., *Epigenesis and Preformationism*. The Stanford Encyclopedia of Philosophy, Edward N. Zalta (ed.), Spring, 2012 Edition.
3. Cfr. GA 733b23 ff.
4. As far as I know the most relevant occurrences of *epigenesis* in Aristotle's *corpus* are the following: *Athenian constitution*: 66, 1, 6; 63, 4, 2; 64, 1, 6; 64, 4, 7; 7, 4, 8; 64, 1, 3; 65, 2, 2; 66, 1, 4; 8, 4, 8; 48, 4, 9. DC: 297a32. *De coloribus*: 795b30; 796a19; 797b27. NE: 1104b4; 1174b33; 1099a26. GA: 730b4; 758b37; 773a17. HA: 633b1; 617b20; 573b18; 580b27; 580b28; 548a13; 558a27; 569b2; 574b16; 603a17; 629a10; 587b34; 631b32; 599b15; 495a28; 504b4; 492b34; 631b12; 499a7. MA: 703b30. Metaph,: 1036b6; 1035a12; 1036a31. *Mirabilium auscultationes*: 834b25; 835b22; 839b28; 833b2; 837a27; 835a14; 840b20; 844a1; 843b17; 843b23. *Oeconomica*: 1347a24; 1349a12; 1346b12. PA: 657b28; 657b24; 681a21; 694a7; 664b22; 665a1; 665a9; 664b25; 665a5. Phys.: 259a2. *Physiognomonica*: 806a8; 806a10; 808b29; 813b13; 811a34. Pol.: 1280b36; 1280b16; 1276a39; 1280a31. *Problemata*: 931a35; 934a26; 859a14; 861b5; 879a16; 966b2; 957a25. *De respiratione*: 479a15; 476a34; 476b3. Rhet.: 1375a10; 1376b5; 1370b25; 1365a24; 1374a1; 1374a2. *Frag*.: 19, 11; 44, 8; 51, 23; 98, 11; 116, 12; 117, 13; 117, 16; 171, 12; 180, 2; 191, 1; 247, 9; 249, 6; 256, 4; 265, 6; 273, 2; 285, 16; 297, 1; 302, 5; 343, 25; 368, 5;

373, 4; 460, 5; 542, 18; 547, 17; 558, 15; 565, 4; 565, 9; 623, 1; 625, 2; 640, 2; 640, 145; 641, 2; 641, 6; 641, 9; 641, 15; 641, 22; 641, 27; 641, 33; 641, 36; 641, 50; 641, 57; 641, 61; 642, 3; 643, 5; 644, 4; 674, 5.

5. GA 730b2-4. All English translations from Aristotle are from BARNES J. (ed.), *The Complete Works of Aristotle: The Revised Oxford Translation*. Princeton University Press, 1984. Cfr.: καὶ εὐθὺς τὴν μὲν ἀθρόον ὑπάρχειν ἀναγκαῖον ἐξ ἧς συνίσταται τὸ κύημα τὸ πρῶτον, τὴν δ' ἐπιγίγνεσθαι ἀεὶ τῆς ὕλης ἴν' αὐξάνηται τὸ κυούμενον.
6. NE 1174b31-1175a3, italics mine. Cfr. τελειοῖ δὲ τὴν ἐνέργειαν ἡ ἡδονὴ οὐχ ὡς ἡ ἕξις ἐνυπάρχουσα, ἀλλ' ὡς ἐπιγινόμενόν τι τέλος, οἷον τοῖς ἀκμαίοις ἡ ὥρα. ἕως ἂν οὖν τό τε νοητὸν ἢ αἰσθητὸν ᾖ οἷον δεῖ καὶ τὸ κρῖνον ἢ θεωροῦν, ἔσται ἐν τῇ ἐνεργείᾳ ἡ ἡδονή· ὁμοίων γὰρ ὄντων καὶ πρὸς ἄλληλα τὸν αὐτὸν τρόπον ἐχόντων τοῦ τε παθητικοῦ καὶ τοῦ ποιητικοῦ ταὐτὸ πέφυκε γίνεσθαι.
7. Rhetoric, 1370b25, italics added by the authors . Cfr.: καὶ ἀρχὴ δὲ τοῦ ἔρωτος αὕτη γίγνεται πᾶσιν, ὅταν μὴ μόνον παρόντος χαίρωσιν ἀλλὰ καὶ ἀπόντος μεμνημένοις [ἐρῶσιν] λύπη προσγένηται τῷ μὴ παρεῖναι, καὶ ἐν πένθεσι καὶ θρήνοις ὡσαύτως ἐπιγίγνεταί τις ἡδονή.
8. Other evidences for this nuance of Aristotle's usage of *epigenesis* can be found in *Metaphysics* 1036a31-1036b7. In this passage Aristotle says that the form *epigignomena* several kind of matter, while naural substances require always the same matter (the so called *oikeia hyle*). Litteraly speaking, this passage could be considered related with an acception of *epigenesis* as 'addiction' of two different elements. However the particular nature of the terms of this 'addiction', their interdipendence, permits to abscribe this passage to other case of supervenience, i.e. as an apparition of a new feature at the end of a gradual change.
9. Aristotle often refers to the differences between change (metabole) and movement (kinesis). Cfr. *De An*. I.3, 406a13 ss.; *Ph*. V.1-3 e VIII.2, 243a8 ss.; *Cael*. IV.3, 310a20 ss. For a first recognition of this argument, see DÜRING I., *Aristoteles: Darstellung und interpretation seines Denkens*. Stuttgart, Druckenmüller, 1968; MULHERN M. M., *Type of Process According to Aristotle*. The Monist 1968; 52(2): 237-251; ROSEN J., *Motion and Change in Aristotle's Physics 5.1*. Phronesis 2012; 57(1): 63-99, but also GIUFFRIDA P. (ed.), *Aristotele. Il movimento degli animali*. Milano, Mimesi, 2012.
10. The term *epigenesis* has often adopted in order to describe Aristotle *idea* about the change occurring in an already existent being. On this argument,

see WARDY R., *The Chain of Change. A Study of Aristotle's Physics VII*. Cambridge (MA), Cambridge University Press, 1990; CASTON V., *Aristotle and supervenience*. The Southern Journal of Philosophy 1993; XXXI(1): 107-135; MASO S., NATALI C. & SEEL G. (Eds.), *Reading Aristotle Physics VII.3. "What Is alteration?"*. Las Vegas, Parmenides, 2012.

11. On Aristotle account of life as dynamic equilibriuum between an internal priciple and exernal stimuli, see WIELAND W., *Die Aristotelische Physik. Untersuchungen über die Grundlegung der Naturwissenschaft und die sprachlichen Bedingungen der Prinzipienforschung bei Aristoteles*. Göttingen, Vandenhoeck & Ruprecht, 1970.
12. See WIELAND W., note 11; but also GRASSO R. & ZANATTA M., *La teoria aristotelica della percezione: temi e problemi*. Milano, Unicopli, 2003.
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