

Is Neanderthal gene introgression into *Homo sapiens* genome an adaptive anti-inflammatory phenomenon that increases depression risk?

Czy zwiększająca ryzyko epizodu depresyjnego introgresja neandertalskich alleli do genomu *Homo sapiens* może być adaptacją przeciwzapalną?

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Abstract

Genes of Neanderthal ancestry are believed to have become incorporated in the modern *Homo sapiens* genome via hybridisation and introgression. Although the majority have been eliminated from the population by natural selection due to Dobzhansky–Muller incompatibilities, some of them nevertheless remain, suggesting they have been selected for and have some adaptive value. The current work examines hypotheses explaining the emergence of depressive symptoms and disorders from an evolutionary standpoint. Neither the incentive hypothesis nor any social hypothesis (social position hypothesis, attachment hypothesis, social navigation hypothesis) accommodates any evidence of archaic introgression. However, the immunological hypothesis, corroborated by a considerable body of research, treats depressive symptoms as part of immunologic response. According to the hypothesis, infections have placed a considerable selective pressure on humans. Upon arrival in Eurasia from Africa, *Homo sapiens* was confronted with unknown pathogenic microorganisms. In contrast, the Neanderthals populating Eurasia had already been adapting to them for millennia. Introgression of Neanderthal man alleles of genes associated with the immunological response has already been demonstrated in *Homo sapiens*, and may well increase the fitness of newcomers. Such inclusion of genes connected with depressive symptoms may explain why archaic alleles are still present in the gene pool of modern humans.

Keywords: depression, psychiatry, affect, biological evolution

Streszczenie

Wykazano, że geny pochodzące od neandertalczyka zostały włączone do genomu współczesnego *Homo sapiens* poprzez hybrydyzację i introgresję. Chociaż większość z nich została wyeliminowana z populacji *Homo sapiens* w wyniku doboru naturalnego z powodu niezgodności Dobzhansky'ego–Mullera, niektóre utrzymały się w puli genowej współczesnego człowieka, co wskazuje na zachowanie ich przez dobór naturalny i pewną ich wartość adaptacyjną. Niniejsza praca analizuje pod tym kątem hipotezy wyjaśniające pojawienie się objawów i zaburzeń depresyjnych z ewolucyjnego punktu widzenia. Ani hipoteza motywacyjna, ani żadna hipoteza społeczna (hipoteza pozycji społecznej, hipoteza przywiązania ani hipoteza nawigacji społecznej) nie daje się powiązać z dowodami archaicznej introgresji. Jednak potwierdzona licznymi badaniami hipoteza immunologiczna traktuje objawy depresyjne jako część odpowiedzi immunologicznej przeciw infekcjom. Zgodnie z nią zakażenia wywierały na człowieka znaczną presję selekcyjną w środowisku adaptacji ewolucyjnej. Po przybyciu do Eurazji z Afryki *Homo sapiens* napotkał nieznaną mu wcześniej mikroorganizmy chorobotwórcze. W przeciwieństwie do niego neandertalczyk zamieszkujący wcześniej Eurazję przystosowywali się do nich przez tysiąclecia. Introgresja neandertalskich alleli genów związanych z odpowiedzią immunologiczną została już wykazana u *Homo sapiens* i mogła znacznie zwiększyć dostosowanie przybyszów. Dotyczy to także genów związanych z reakcją depresyjną. Takie włączenie alleli genów związanych z objawami depresyjnymi może wyjaśnić, dlaczego związane z objawami depersyjnymi archaiczne allele są nadal obecne w puli genowej współczesnego człowieka.

Słowa kluczowe: depresja, psychiatria, nastrój, ewolucja biologiczna

INTRODUCTION

Background and hypothesis

Neanderthal man (*Homo neanderthalensis*) is a separate species in the genus *Homo*, described by King in 1864 (King, 1864). Over time, debate concerning the extinction of Neanderthals began to discuss possible hybridisation between Neanderthals and the ancestors of modern man (Smith et al., 2005). Nowadays, hybridisation is considered a proven fact: 2% of the genetic material of modern humans descending from Eurasia, so-called archaic gene alleles, is believed to have been inherited from Neanderthals (archaic introgression) (Fu et al., 2016). Originally, it was 3.2–5.7% (Fu et al., 2016), however multiple archaic gene alleles have been eliminated from the modern human gene pool by natural selection, probably due to Dobzhansky–Muller incompatibilities (discrepancies between gene alleles from genetically-distant populations), causing especially male sterility, as evidenced by gene deserts, especially on the X chromosome (Sankararaman et al., 2014). Moreover, some papers have described specific archaic alleles of definite genes in the *Homo sapiens* genome. Dannemann and Kelso (2017) listed genes linked to skin and hair colour, immune system and metabolism, and propose that archaic gene alleles may be connected to symptoms of mood disorders (two-week-lasting unenthusiasm, loss of interest, social isolation), circadian rhythm, nicotine addiction, skin lesions, and coagulation disorders. Simonti et al. (2016) also indicate that Neanderthal genes may be associated with the risk of depressive disorder and mood disorders in general, tobacco use, hypercoagulation linked do factor V, and skin lesions, especially actinic keratosis.

Consecutive papers examining both Neanderthals and Denisova men, regarded by some as another distinct archaic species, subspecies or population of humans, have proved multiple archaic introgression events (Gokcumen, 2020). It was proposed that alleles of a number genes associated with the immune system (e.g. *SELP*, *OAS*, genes coding HLA, Toll-like receptors – TLRs and linked to cytokines) may have archaic ancestry, including the ones connected with Crohn's disease or coeliac disease (Dolgova and Lao, 2018), as well as those linked to chronotype (*ASB1*) (Dannemann and Kelso, 2017). Some archaic gene alleles were preserved in the modern human gene pool due to adaptive introgression (particularly the archaic gene alleles enhancing fitness) or balancing selection, i.e. natural selection maintaining multiple alleles of some gene in the gene pool, alleles diversity enhances fitness. That group comprises genes linked to the immune system (*HLA*, *STAT2*, cluster *OAS*), pigmentation (*HYAL2*, probably *BNC2*) and keratinocytes (*POU2F3* and neighbouring transmembrane protein-coding *TMEM136*), adaptation toward hypoxia (*EPAS1*), lipid metabolism (*SLC16A11*, *SLC16A13*), and the *DMD* gene (Racimo et al., 2015).

Taking into consideration the widespread natural selection against archaic gene alleles in the *H. sapiens* gene pool (Gokcumen, 2020), the following question arises: how have archaic gene alleles associated with depressive symptoms been preserved? We hypothesise that the aforementioned alleles have been maintained in the modern human gene pool because they somehow enhanced fitness, i.e. represent another example of adaptive introgression or balancing selection.

This sphere of research is of interest to evolutionary psychiatry. The presented study attempts to connect genetic data concerning archaic introgression with the achievements of evolutionary psychiatry.

Evolutionary psychiatry

Evolutionary psychiatry tries to explain the occurrence of mental disorders from an evolutionary standpoint, especially using concepts and methods derived from evolutionary biology. It addresses the paradox of why genes connected with the development of mood disorders, and even mental diseases, are not removed from the population by natural selection together with other seemingly unfavourable characteristics (Nowak, 2017). In the field of mood disorders, evolutionary psychiatry is particularly concerned with depressive disorders. It is now widely accepted that such disorders have at least partial genetic background, and connections between genes and depressive disorders have been described in numerous studies and meta-analyses (López-León et al., 2008). Depressive disorders lower fitness by exerting a negative effect on survival, for example by raising the risk of suicide (Isometsä, 2014) and impairing reproduction (Williams et al., 2007). It would be reasonable to assume that such harmful gene variants would be eliminated from the population over time due to natural selection mechanisms. For example, the fraction of Neanderthal genes in in *H. sapiens* has been decreasing over time since the extinction of Neanderthals, and thus the end of hybridisation (Fu et al., 2016).

The persistence of genes linked to depressive disorders in the population has been explained by various hypotheses proposing mechanisms based on the possible positive effects that depressive symptoms or related phenomena could exert on fitness. The following paragraphs will focus on determining whether the presence of Neanderthal DNA in the modern human genome contributes to the evolutionary hypotheses of depressive disorders.

METHODS

A PubMed search was performed with the following keywords (used with Boolean operators): “depressive disorder” AND (evolutionary OR evolution) to examine the emergence of depressive symptoms and disorders from an evolutionary standpoint. Only papers with full text published in English or Polish were taken into account. No publication date limits were administered. Research was under-

taken initially in December 2020 and followed up in 2022. The following hypotheses were found: the incentive hypothesis, the attachment hypothesis, the social rank hypothesis, the social navigation hypothesis, and the immunological hypothesis. These are discussed in the present study.

RESULTS

Evolutionary hypotheses of depressive disorders

According to the **incentive hypothesis** of depressive disorder, depressive symptoms are not able to exert any positive effect on fitness. They are more analogous to pain, which can serve as reinforcement for the organism and discourage it from taking up the activity that caused the pain. In the same way, depressive symptoms should act as strong motivators to avoid certain activities, particularly those that reduce fitness; in fact, even the mere observation of depressive symptoms in another person, or the potential to imagine suffering from such symptoms, would also discourage participation (Wittman, 2014). However, this hypothesis depends heavily on the learning speed of *H. neanderthalensis* and the degree to which it differs from that of *H. sapiens*. A range of **social hypotheses** have also been proposed; these have been grouped according to an evolutionary hypotheses of depressive disorders classification proposed by Gilbert (2006). The evolutionary formulation of Bowlby's (1969) **attachment theory** compares the behaviour of a depressive person to that of a juvenile human, or another mammal, left alone by the mother. Withdrawal or decreased psychomotor drive forces the child to wait calmly until the mother returns, thus remaining unnoticed by potential aggressors. A similar tendency sustained into adulthood would result in the occurrence of depressive episodes. Such behaviour is common to many mammal species and can be assumed to apply equally to modern man and Neanderthals.

Similar conclusions can be drawn from an analysis of the **social rank hypothesis** (Muntaner et al., 2004). Assuming that a greater incidence of depressive symptoms tends to be observed in people of lower social status, the hypothesis proposes that these symptoms serve to signal subordination and hence avoidance of competition with those of higher status: taking up such a challenge rarely results in victory, and the costs of a confrontation outweigh the benefits. As a result, those of higher status do not have to emphasise their dominance, thus avoiding combat and enhancing the overall functioning of the hierarchical group.

Behaviours resembling depressive symptoms, as well as abnormalities of the serotonin system and hypothalamus–pituitary–adrenal axis associated with depressive symptoms, have also been observed in catarrhine monkeys (Levitan et al., 2000), suggesting that the described mechanism acts in a similar way in humans and other primates. The more advanced development of the human encephalon results

only in the construction of a more sophisticated level of social relations. The hypothesis would, therefore, describe both modern humans and Neanderthals.

Finally, the **social navigation hypothesis** proposes that depressive symptoms are influenced by the social rumination function, i.e. limiting other activities and spending all available energy on resolving a difficult and preoccupying solution, and the social motivation function: the members of a small social group are forced to help a group member presenting depressive symptoms not only to ensure the fitness of the individual, but also their own (Watson and Andrews, 2002). However, as in the case of the other hypotheses discussed above, it is not clear what new implication could be brought to it by information about Neanderthal DNA in *H. sapiens* cells. In contrast, it is possible that genetic bases may exert an impact when considering the immunological hypothesis of depressive disorder.

Immunological hypothesis

This hypothesis is based on numerous studies suggesting that the immune system of people suffering from depressive symptoms acts in a different way than those of people who are not depressed. These healthy controls tend to be recruited for the studies by various methods, such as a newspaper announcement (Suarez et al., 2004) or during a medical visit for some other indication, such as pregnancy (Christian et al., 2010). It has been found that both people with mild forms of affective disorders, such as seasonal affective disorder (Song et al., 2015), and patients diagnosed with major depressive disorder (Lin et al., 2018) demonstrate differences in immune system functioning compared to unaffected people.

Depressive symptoms have been found to co-occur with many indicators of inflammation, such as increased plasma levels of pro-inflammatory cytokines, including interleukins 1 β , 2, 6, tumour necrosis factor (TNF), and various chemokines (Lin et al., 2018; Raison et al., 2006), acute phase proteins, such as C-reactive protein (CRP), α 1-antichymotrypsin, α 1-acid glycoprotein, and adhesive particles, such as monocyte chemoattractant protein-1 (MCP-1), soluble intracellular adhesion molecule-1 (sICAM-1), selectin E (Raison et al., 2006). They have also been associated with enhanced expression of genes coding interleukins 1 α , 2, 3, 5, 8, 9 and 10, but not the anti-inflammatory forms including interleukin 12A, 13, 15, 18, γ interferon and α lymphotoxin in the prefrontal cortex (Raison and Miller, 2017). Different reactions have also been observed following antigen stimulation, with the immune response generally increasing in severity with the presence and severity of depressive symptoms (Christian et al., 2010; Suarez et al., 2004); however, decreased reactivity has also been observed (Lin et al., 2018). Disparities were found in leukocyte subpopulations as well (Song et al., 2015). Inflammation stimulates the activity of the tryptophan-decomposing enzyme indoleamine-2,3-dioxygenase (IDO), thus

resulting in a greater production of the neurotoxic kynurenine at the expense of the neuroprotective kynurenin acid, and hence the possible emergence of depressive symptoms (Dantzer et al., 2011).

The **revised form of the PATHOS-D (Pathogen Host Defence) hypothesis** (Raison and Miller, 2017, 2013) proposes that not only does inflammation result in depressive symptoms, but also depression-causing factors stimulate immune system activation, and hence pro-inflammatory cytokine synthesis. The authors put forth three ways by which the blood–brain barrier (BBB) may be circumvented to allow access of these factors to the central nervous system: leakage due to inflammation, entry via the vagus nerve or entry through areas of greater BBB permeability in the choroid plexus. The latter hypothesis is supported by changes in the expression of immune system-related genes, such as those coding 1 β , ICAM1, IBA1 (ionised calcium-binding adapter molecule 1), in the choroid plexus of suicide victims. This has been interpreted as downregulation caused by persistent immune system activation (Devorak et al., 2015). However, this observation raises the question of whether inflammation and inflammation-linked predisposition to mood disorders have any evolutionary significance.

Raison and Miller (2013) note that infections, as well as the need for effective immunity to infection, place a significant selection pressure on the evolution of humans and other animal species, as these have significant effects on mortality, especially in primitive communities. In their view, depressive symptoms caused by infection and inflammation should enhance immunity. The mechanism they describe resembles the one proposed earlier by Kinney and Tanaka (2009), which states that apathy, decreased psychomotor drive or psychomotor retardation, anhedonia, interest loss and drowsiness are needed to save the energy necessary to fight infection, to avoid dangerous situations or the risk of contracting another infection. A lack of appetite limits the energetic cost of digestion, and protects from potential superinfection by contaminated food. A craving for sugar should encourage the consumption of food containing alcohol or honey, which can have antimicrobial and immunomodulatory properties. Low self-esteem protects the individual by discouraging engagement in competition in poor health. In addition, social isolation associated with depression and sending social signals that discourage interpersonal contact (sadness expressed by facial mimics and body posture, irritability) prevents the transmission of infection to relatives. Similar behaviour, i.e. sickness behaviour, is also observed in many vertebrate species.

On the other hand, the stressors present in the evolutionary adaptedness environment, i.e. the environment in which human evolution has taken place for most of its history (Rybakowski and Rybakowski, 2003), are most often linked to the risk of trauma and infection, such as while hunting or fighting a wild animal, or another hostile individual of the same species. A more precise description, together with detailed criticism, can be found in an excellent review of

this paper (Raison and Miller, 2017). The reviewers provide a concise discussion of the influence of genes believed to have entered the *H. sapiens* genome by introgression from *H. neanderthalensis* on the emergence of depressive symptoms and immune system functioning; they also highlight disparities in the occurrence of genes influencing depressive symptoms between different human groups, and mention the possible role played by the initial encounter with European pathogens. However, they do not elaborate on the last issue.

Evolutionary history of *H. sapiens* and *H. neanderthalensis*

Mitochondrial DNA research suggests that the evolutionary lines involving modern humans and Neanderthals separated approximately 398,000 years ago (95% confidence interval: 295–498) (Rieux et al., 2014). However, it is also believed that the first representatives of *H. sapiens* reached Europe earlier.

Raison and Miller (2017) discuss the significant diversity of depressive symptoms-related genes reported in different populations in the light of the immunological hypothesis. They attempt to account for such genetic disparities by referring to differences in selective pressure exerted by pathogenic microorganisms on different human populations. This pressure is believed to play a crucial role in evolution (Fumagalli et al., 2011). It is likely that while spreading across Europe, the Neanderthals came into contact with new microorganisms, including some exclusive to the colder climate of northern Europe, and had to evolve effective coping mechanisms. No such selective pressure was experienced at that time by *H. sapiens* in Africa, which had already adapted to the local microbial flora; this claim of course assumes the *out of Africa* hypothesis, which is widely considered as a proven fact, but sometimes also criticised (Árnason and Hallström, 2020).

However, *H. sapiens* would also have contacted unknown pathogenic microorganisms upon entry into Europe, in a similar way to the first encounters between the indigenous American people and the infectious diseases carried by Europeans, who had developed immunity to them (Walker et al., 2015). *H. sapiens* would also have encountered *H. neanderthalensis* and Denisovan for the first time, and hybridisation between the two species is proven: such phenomena are widely observed in cases involving two closely-related sympatric species. Unfortunately, as genes belonging to the same gene pool evolve together and natural selection usually maintains gene variants which cooperate best with each other, the offspring of interspecific couples typically have poorer fitness than the parents: they tend to live shorter lives and have a lesser chance of having offspring themselves (Schumer et al., 2018), a phenomenon known as Dobzhansky–Muller incompatibilities. In this way, a major part of the Neanderthal DNA in the *H. sapiens* gene pool was probably eliminated.

However, transmission of the Neanderthal genes bestowing a better response to infection, and thus counteracting the main cause of premature death more effectively, may outweigh the fitness cost associated with poorer cooperation between genes (adaptive introgression). The Neanderthal origin of *H. sapiens* genes connected with immune response was confirmed. That genes might have reached the *H. sapiens* genome due to introgression; this group includes genes coding for HLA and STAT2 (Racimo et al., 2015), the *OAS* gene (Mendez et al., 2013) and those coding for TLRs (Quach et al., 2016). Moreover, archaic haplotypes associated with protection against infection were found in modern human genome, e.g. against the West Nile virus, hepatitis C virus, but also a haplotype on chromosome 12 associated with protection against severe COVID-19 (Zeberg and Pääbo, 2021) [in the case of this newly evolved coronavirus, other archaic haplotypes became risk factors for severe symptoms (Zeberg and Pääbo, 2020)].

According to the immunological hypothesis, the depressive symptoms-associated genes can also have a positive influence on fitness by taking part in the immune response. Thus, the immunological hypothesis may account for the broader description of depressive disorders and explain the Neanderthal origin of genes related to affective disorders. Moreover, the evolutionary benefits associated with the introgression of immunity-regulating genes accounts for the maintenance of genes predisposing to depressive disorders in the *H. sapiens* gene pool.

DISCUSSION

The immunological hypothesis of depressive disorders appears to account not only for the concomitance of depressive symptoms and inflammation markers observed in numerous research studies, but also draws in data from the seemingly distant field of science exploring the genetic traits of hominid evolution and origin of *H. sapiens*. It also appears coherent with the results of studies concerning introgression. Nevertheless, it still remains a hypothesis: even though it can account for a considerable number of observations, it still copes poorly with predicting new ones. Furthermore, as with other efforts to explain psychiatric disorders on the basis of evolutionary biology, the immunological hypothesis has little support in the scientific community, as scientists are more preoccupied by proximal explanations, focused on pathophysiology (Nesse, 1999). Despite serving as an accepted basis in the biological sciences, the evolutionary paradigm, in the form of modern evolutionary synthesis, is not popular in medicine. It includes numerous scientific theories, but predictions based on them are difficult to confirm or refute with the methodology commonly used in medicine.

Moreover, although some studies point towards the Neanderthal DNA introgression into the *H. sapiens* genome in a general sense, relatively few papers have examined the Neanderthal origin of particular genes. The significance of

these findings can change in the broader context, and hence requires further confirmation.

The demonstrated hypothesis postulates that the genome of modern *H. sapiens* includes genes related to the occurrence of depressive symptoms derived from Neanderthals; however, it would be incorrect to assume that modern man also inherited depressive disorders from Neanderthals. For example, while it is possible to make inferences about the possible skin and hair colour of Neanderthals on the basis of various alleles passed to modern-day Europeans by introgression, the lack of a direct relationship between genotype and phenotype prevents any accurate prediction of true skin or hair colour (Dannemann and Kelso, 2017). In the case of depressive episodes, these would have more far-reaching ramifications. Regarding sickness behaviour, i.e. behaviour connected to infection, comprising *inter alia* social withdrawal, decreased activity and fasting, which has been widely compared to the behaviour typical of depressive episodes, there is no proof that in *H. neanderthalensis* it was accompanied by any phenomenon absent in other mammal species (though this assumption cannot be rejected, either). It is possible that the genes linked to sickness behaviour in Neanderthals began to function differently in the new environment of the alien genes of the *H. sapiens* genome, characterised by poorer mutual cooperation; this lack of cooperation may have resulted in the occurrence of depressive episodes that were more prolonged and intense with regard to sickness behaviour in Neanderthals. Alternatively, Rybakowski and Rybakowski (2003) refer to the concept of an environment of evolutionary adaptedness, in which the discussed genes worked to form the most adaptive traits; in this case, the genes became maladaptive only when important environmental changes had been made by humans. Finally, Simonti et al. (2016) propose that among the *H. sapiens* genes of Neanderthal origin, the loci connected with the circadian rhythm may have a significant influence. Their hypothesis suggests that alleles received due to introgression have some adaptive value; however, this value is associated with the regulation of sleep and wakefulness rather than the immunological system. Neanderthals could have developed adaptations to the shorter days and long dark winter evenings in the temperate climate, which had not been faced by *H. sapiens* in Africa. However, the positive effect exerted on fitness by better adjusted circadian rhythm does not rule out other mechanisms. Genes often act in pleiotropic way, via concerted actions employing different mechanisms. A similar hypothesis concerning Neanderthal introgression was put forth to explain the origin of bipolar disorder. The hypothesis of the evolutionary origin of bipolar disorder-revised (EOBD-R) formulated by Sherman (2012) states that bipolar behaviour appeared in Neanderthals as an adaptation to severe Pleistocene climatic conditions in the temperate zone. It treats winter depression as an adaptation to northern winters, along with Neanderthal pyknic cold-adapted body build and hibernation (Bartsikas and Arsuaga, 2020).

Although no direct connection between depression and Neanderthal gene introgression was found in an extensive genome-wide population study (Dannemann et al., 2022), the same investigation identified significant relationships with behavioural phenotypes, including pain, chronotype/sleep, smoking, and alcohol consumption. The relationship between major depression epidemiology and behavioural phenotypes was repeatedly observed, including the sleep chronotype (Garbazza et al., 2022), smoking (Fluharty et al., 2017), alcohol consumption (Schick et al., 2022), and pain (IsHak et al., 2018). Thus the link between Neanderthal gene introgression and depression may be indirect, taking place via mediators that are not yet known.

CONCLUSIONS

Among the few existing evolutionary hypotheses of depressive disorders, the immunological hypothesis is the only one that addresses the findings of numerous studies confirming the relationship between the presence of inflammatory markers and depressive symptoms. It is also the only one to account for the introgression of Neanderthal genes into the *H. sapiens* genome. Nonetheless, perhaps due to it being based on the evolutionary paradigm, unpopular in the medical sciences, the immunological hypothesis remains poorly explored, which is why it remains a hypothesis. Therefore, further studies are needed before the discussed hypothesis can enjoy wider acceptance or rejection.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations that could negatively affect the content of this publication and claim authorship rights to this publication.

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