

Evolutionary approaches to autism- an overview and integration

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ABSTRACT: Autism is a highly heritable neurodevelopmental disorder, which greatly reduces reproductive success. The combination of high heritability and low reproductive success raises an evolutionary question: why was autism not eliminated by natural selection? We review different perspectives on the evolution of autism and propose an integration which emphasizes epistatic interactions between the effects of genes during development. It is well-established that autism is a polygenic disorder, and that the genes contributing to autism interact. If a disorder is polygenic, it is likely that the genes underlying the disorder are also involved in traits that are beneficial for the individual. For example, it is possible that genes involved in the development of autism are also involved in the development of intelligence. As intelligence is positively correlated with reproductive success, genes involved in autism can possibly spread in the population. We propose that in most individuals, the interactions between genes result in normal or high intelligence and the absence of autism. However, in some unlucky situations, often in combination with spontaneous negative mutations, the interactions between genes can lead to the development of autism (or other pathologies). Thus, the combination of high heritability and low reproductive success in autism can be explained from an evolutionary developmental perspective that emphasizes the role of epistatic interactions in polygenic disorders.

Keywords: Autism, evolutionary psychology, heritability, epistasis

INTRODUCTION

Autism is a highly heritable neurodevelopmental disorder (1-2), with deleterious effects on reproductive success (3). The combination of high heritability and low reproductive success raises an evolutionary question (4): why was autism not eliminated by natural selection? In this paper we present an overview of theories that address the evolution of autism, and we formulate an integration of these different theories.

Autism as the result of an extreme male brain

The extreme male brain theory of autism postulates that affected individuals are extremely focused on systemizing as opposed to empathizing (5-6). Men, on average, appear to have a more systemizing brain than women, i.e., they are more interested in and better at analyzing variables in a system, and at deriving the rules that govern the behavior of a system. Women, on the other hand, seem to have a more empathizing brain, i.e., they are better at inferring mental states in other people, and to respond appropriately to these mental states. Empirical support for the extreme male brain theory of autism comes from several sources. First, more males are affected by autism than females (7). Second, high-functioning affected individuals

(i.e., with an average or above average IQ) tend to outperform unaffected people with similar IQs on systemizing tasks (8). Third, the behavioral differences between people with and without autism are mediated by differences at the anatomical level of the brain (9). Fourth, prenatal exposure to testosterone (i.e., an androgen) is positively related to the development of autistic traits (10).

From an evolutionary point of view, in ancestral times, men with well-developed systemizing skills and under-developed empathizing skills may have had an advantage over other men (11). It is generally accepted that most humans used to live in hunter-gatherer societies, in which men fulfilled the role of hunter, and women the role of gatherer. Systemizing may have been important in developing tools and weapons, in hunting, tracking, and trading. Empathizing may have been disadvantageous in situations where rivals had to be eliminated, and in situations where one had to tolerate solitude, while being far away from home for hunting. For women, empathizing may have been more important because of mothering, making new friends (women used to marry into new groups), gossiping, and inferring the thoughts of a possible mate (to discover whether he is willing to invest in offspring). So having an extreme male brain, a condition which we strongly associate with autism, may have had practical advantages given demands of ancestral times. These advantages would have conferred greater reproductive success, thus ensuring the continued existence of this condition.

Autism as the result of an extreme imprinted brain

A second theory on the evolution of autism is the imbalanced genomic imprinting theory (12). Genomic imprinting refers to the expression of genes from only one of the two parental chromosomes (13). We inherit two copies of every allele, a maternal and a paternal copy. In most cases both copies are functional, but in some exceptional cases one of the copies is turned off (i.e., silenced) and thus not functional. This may be the consequence of imprinting: maternal imprinting ensures that only the maternal copy is expressed, and paternal imprinting ensures that only the paternal copy is expressed. Imprinted genes show 'parent-of-origin effects' in the inheritance of traits: maternally expressed genes are inherited down the matriline, whereas paternally expressed genes are inherited down the patriline.

The evolutionary function of imprinted genes is unknown. It has been suggested that genomic imprinting originates in a conflict between the sexes about the amount of investment of the mother in the child (14). Paternally expressed imprinted genes tend to promote fetal growth, whereas maternally expressed imprinted genes tend to suppress fetal growth. From the father's point of view, it is beneficial that the mother invests as much as possible in the child. From the mother's point of view, it is important to preserve her resources. This implies that it is beneficial for her to invest in the child only as much as is necessary.

It has been shown that imprinted genes are highly expressive in the central nervous system, and that they are involved in neurodevelopment (15). There is some evidence that maternally imprinted genes are expressed in the cerebral cortex and hippocampal regions, brain areas involved in cognitive processing, whereas paternally imprinted genes are expressed in the hypothalamic and septal brain areas (16), brain areas involved in emotional processing; however, this finding has not been replicated (17). Imprinted genes are often implicated in disorders, because a single change can dysregulate their function (18-19). Genomic imprinting has been linked to several disorders, including autism. Crespi and Badcock hypothesized that autism reflects reduced maternal brain functions, and enhanced paternal brain functions (12). This hypothesis is supported by the sex ratio in autism; more males are affected than females (7). A second source of evidence is provided by genome scans, which show that many of the genes involved in autism contain imprinted genes or genes that interact with imprinted genes (12).

Crespi and Badcock suggested that autism is the low-fitness extreme of a condition that is beneficial for the father (20). Children with autism impose additional demands compared to normal children, especially on mothers, who tend to be the primary caregiver. These demands include dealing with tantrums, attempts to control others, lack of cooperative behavior, and lack of empathy. Normal children who display such behavior also impose additional demands on the mother, which is beneficial from the point of view of the father, because the mother will spend more of her time and resources on the child. However, in the case of autism, the behavior of the child assumes pathological proportions which no longer benefit either the mother or the father.

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Autism as a low-fitness extreme of a parentally selected fitness indicator

A third theory postulates that autism is the low-fitness extreme of a parentally selected fitness indicator (21). A fitness indicator is a trait that takes considerable energy to develop, maintain, and display. This cost makes it a reliable indicator of fitness, because the energy demands ensure that the indicator characterizes mainly the individuals who are sufficiently fit to meet them. The peacock's tail is a famous example of a fitness indicator that does not contribute to survival, but does help to attract mates. The peacock's tail is a sexually selected trait. It is likely that there are also parentally selected fitness indicators; parents are likely to invest more of their resources in offspring that are more likely to survive and reproduce. Thus, it is possible that parental selection resulted in offspring traits that evolved to win parental resources. Shaner and colleagues proposed that parental selection could have caused some aspects of the social repertoire of infants to evolve as a fitness indicator and that autism could represent its low-fitness, poor quality extreme. They termed the overall trait 'charm' and suggested that it may include babbling, smiling, and creative play. Infants that are characterized by high genetic quality (i.e., a low mutation load) and that are reared in a favorable environment would be able to develop the complex brain systems required for highly charming behavior. Infants that are characterized by low genetic quality (i.e., a high mutation load) would not be able to develop these complex brain systems as well, therefore would not display the charming behaviors (at least not to the same degree). In a few, the behavioral deviations would be so severe that we would associate them with autism. Evidence for this theory is that infants develop charm at the time when mothers start to show signals of weaning (22), and that autism is correlated with early weaning (23).

Autism as the result of a reptile brain

A different perspective on the evolution of autism is provided by the Polyvagal theory (24). Polyvagal theory postulates that through three stages of phylogeny, mammals, especially primates, including humans, have evolved a functional neural organization that regulates emotions and social behavior. The vagus, i.e., the 10th cranial nerve is a major component of the autonomic nervous system that plays an important role in regulating emotions and social behavior. The three stages of phylogeny reflect the emergence of three distinct parts of the

autonomic nervous system, each with a different behavioral function. In the first evolutionary stage, the unmyelinated vagus emerged, which regulates immobilization for death feigning and passive avoidance. These are typical responses to dangerous situations in reptiles, but atypical in mammals, including humans. In the second stage, the sympathetic-adrenal system emerged, which is characterized by mobilization as a response to dangerous situations. In the third stage, the myelinated vagus emerged, which is involved in social communication, self-soothing and calming. It is proposed that people with autism minimize the expression of the mammalian response, i.e., social communication. Rather, they rely on the defensive strategies that include both mobilization and immobilization.

While normally primates and humans have a well-developed ability to shift adaptively between mobilization and social engagement behaviors, individuals with autism lack this ability. The resulting behavioral features lead to adaptive benefits in focusing on objects, while minimizing the potentially dangerous interactions with people. Without a readily accessible social engagement system, the myelinated vagus is unable to efficiently inhibit an autonomic state and is poised for flight and fight behaviors with the functional outcomes of frequently observed emotional outbursts or tantrums. The combination of a nervous system that favors defensive behaviors, and the inability to use social communication with people, places the autistic individual outside the realm of normal social behavior. Thus, due to the inability to engage the myelinated vagus to calm and dampen the defensive system (through social interactions), the nervous system of the autistic individual is in a constant state of hypervigilance or shutdown. These are generally adaptive responses in reptiles, but are severely maladaptive in mammals.

Towards an integration of different approaches on the evolution of autism: Autism as the result of epistatic interactions between the effects of genes

Each theory described above has its merit; each theory explains some part of the phenotype of autism, and is supported to various degrees by empirical evidence. Is it possible to integrate these theories to arrive at a sensible account for maintenance of a highly heritable disorder, which is characterized by low reproductive success?

It is well-established that autism is caused by many interacting genes (25-26). As nearly 30

genes have been associated with autism (27), autism is clearly no Mendelian (single gene) disorder. An evolutionary theory of autism should take into account the developmental effects of both its polygenic nature and of interactions among the genes (i.e., epistatic interactions) (28). Assume that there are 30 genes involved in the development of autism (this number is likely to be larger), and that this same set of genes is involved in the development of intelligence. Given the evidence that intelligence is positively correlated with potential reproductive success (29), the 30 genes that are involved in autism can potentially spread in the population, thanks to the link with intelligence. In most people, interactions between these 30 genes result in an individual with normal or high intelligence, without autism. However, some unlucky interactions, especially in combination with negative spontaneous mutations (30-31), lead to the development of autism, low intelligence, or other pathologies. With regard to autism, the unlucky effects of interactions between genes are negatively correlated to survival (32) and reproductive success (3). However, most of the time, interactions between the 30 genes lead to higher fitness (because of higher intelligence), and consequently, genes involved in autism can be beneficial. Thus, the combination of high heritability and low fertility in autism can be explained from an evolutionary developmental perspective that emphasizes the role of epistatic interactions in polygenic disorders.

There are several lines of evidence that support this idea. The first line concerns the relation between autism and intelligence or other exceptional abilities. A behavioral genetic study showed that there is substantial overlap between genetic factors that influence individual differences in autistic traits and intelligence (33). In addition, on certain intelligence tests, individuals with autism show equal or better performance levels compared to normal individuals. These tests include the Raven's Progressive Matrices test (34) and the block design test (35). There is also evidence for the relation between autism and exceptional abilities, with some famous examples of autistic savants (36-37). The co-occurrence of savant syndrome and autism is an example of the effect of epistatic interactions between genes, in which potentially beneficial effects of genes are nullified by the negative effect of autism, mental retardation, or other disabilities, on reproductive success (38).

The second line of evidence is the relation between assortative mating and autism (39).

Assortative mating refers to the tendency of mating with individuals who are phenotypically similar. It was found that mothers and fathers of children with Asperger syndrome, one of the autism spectrum disorders, scored highly on the Embedded Figures test, a test that is often included in IQ test batteries (40). Both mothers and fathers of children with Asperger syndrome tend to have jobs that require high intelligence (41). Other studies revealed a positive correlation between the score of fathers and mothers of children with autism on measures of autistic traits (42-43), although another study did not confirm this (2).

A third piece of evidence for the involvement of epistatic interactions between genes in autism is the co-occurrence of autism and several other disabilities. There is ample evidence that autism co-occurs with medical syndromes (44), and minor physical anomalies (45). There is also considerable comorbidity with other psychiatric conditions (46). Epistatic interactions between the effects of genes can explain the diverse array of phenotypes associated with autism spectrum disorders: in people with severe autism, which often co-occurs with mental retardation and physical disabilities, the effects of interactions between genes are extremely unlucky and most likely co-occur with spontaneous mutations.

The proposal that the combination of high heritability and low fertility in autism can be explained by the effects of epistatic interactions between genes that are involved in both intelligence and autism, provides an integration of the different approaches to the evolution of autism discussed above. The extreme male brain theory of autism is consistent with this proposal, as systemizing can be regarded as a subset of intelligence. The extreme imprinted brain theory of autism can also be integrated in the proposal, as imprinted genes are known to be highly epistatic (47). The theory that autism is a low-fitness extreme of a parentally selected fitness indicator is also consistent with the proposal, as it is likely that unlucky combinations of genes result in detectable indications that the individual is not fit. The co-occurrence of autism and syndromes is an example, but these signals can be more subtle, such as physical asymmetry. Some evidence suggests that autism is positively related to asymmetry (48-49), with symmetry being regarded as a signal of high fitness (50). Finally, the theory of autism as a consequence of a reptile brain describes what may have gone wrong with the brains of people with autism at the neurobio-

logical level, and how this can be explained from a phylogenetic point of view. It does not explain the genetic background and the heritability of autism, so the reptile brain theory needs some extension to give a full explanation of the evolution of autism. The theory is not in disagreement with the idea that autism is the result of epistatic interactions between the effects of genes, so combining the two ideas may lead to a more complete account of the evolution of autism.

To sum up, this paper proposed a new theory that may explain the evolution of autism, which is a puzzle because of the combination of high heritability and low reproductive success. Epistatic interactions between potentially beneficial effects of genes may lead to unlucky gene expression that eventually leads to the development of autism. Earlier theories on the evolution of autism are not necessarily in disagreement with this new theory, but the new theory may serve as an integrative framework for different views on the evolution of autism.

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