Rethinking schizophrenia through the lens of evolution: shedding light on the enigma

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Abstract

Schizophrenia refers to a complex psychiatric illness characterized by the heterogenic presence of positive, negative and cognitive symptoms occurring in all human societies. The fact that the disorder lacks a unifying neuropathology, presents a decreased fecundity of the affected individuals and has a cross-culturally stable incidence rate, makes it necessary for an evolutionary explanation that fully accounts for the preservation of “schizophrenic genes” in the global human gene pool, explaining the potential sex differences and the heterogeneous cognitive symptomatology of the disorder and is consistent with the neuropsychological, developmental and evolutionary findings regarding the human brain. Here we proposed a new evolutionary framework for schizophrenia that is consistent with findings presented in different dimensions, considering the disorder as a form of brain functioning that allows us to adapt to the environment and, ultimately, maintain the survival of the species. We focus on the epigenetic regulation of thalamic interneurons as a major player involved in the development of the clinical picture characteristic of schizophrenia.

Keywords

schizophrenia; evolution; human thalamus; interneurons
Introduction

Schizophrenia is considered as a debilitating genetic psychiatric disorder characterized by the presence of a constellation of symptoms that fits into three categories that affects all the cognitive domains described to date. In the last ten years, the number of papers about the molecular biology, anatomy, physiology or cognition, among other aspects, of schizophrenia has increased until reaching an average of, approximately, 5,000 works per year. Most of which have been presented as major breakthroughs that are impossible to replicate, resulting in a data accumulation that clearly reflects a sign of uncertainty and confusion (Maj 2011). While Maj suggests that in our understanding of the pathophysiology of schizophrenia we must ask ourselves if we are on the wrong or on the right track (Maj 2011), we think that we need to include different aspects of the two tracks to understand why we fail when we try to understand and explain, in Jaesperian terms, this complex phenomenon.

We cannot deny that we are facing a complex issue with several edges, many of them enigmatic (Alelu-Paz et al. 2016) which, together, create an unresolved pool of questions such as: Why has natural selection allowed genes to persist in the human genome that increase the likelihood of suffering schizophrenia, despite its reproductive disadvantage? Can we describe a disease entity corresponding to what we call schizophrenia? Is there an exact correlation between genotype and phenotype? What role do environmental factors play in schizophrenia etiology? Is there a link between brain malfunctioning and schizophrenia symptoms?

Let's start with one of the most significant contributors in the past 25 years: the neurobiology approach.

What do we know about the neurobiology of schizophrenia?

Classically, we define schizophrenia as a complex psychiatric illness occurring in all human societies with approximately the same incidence (Crow 1995b) and with a high heritability (between 60 and 80%) (Lichtenstein et al. 2009). Adolescence and early adulthood represent the critical time period when the first symptoms appear, with a median lifetime prevalence of 4.0 per 1000 that seems to remain stable across generations (Srinivasan et al. 2016), a morbid risk of 7.2 per 1000 (Cariaga-Martinez et al. 2016), a reduced fecundity of, around, 50% compared to healthy individuals (Brune 2004, Power et al. 2013) and mortality rates significantly greater than in the general population (Liu et al. 2017, Saha et al. 2007).

The idea that schizophrenia is a brain disorder and, therefore, it is possible to study the neurobiological bases of the clinical symptoms that the diagnosis is based on, it has been translated into a paradigm shift, giving primacy to neurochemical and molecular perspectives to the detriment of those that understand it as a psychological reactions to stressful environments (Mathalon and Ford 2012). Both approaches have always been considered, in some way, incompatible and, both, largely unsuccessful. It is important to
highlight that schizophrenia is influenced by a set of several genetic and environmental factors that genetics alone cannot explain. What’s more, neurobiology has not been able, until today, to explain the phenomenon; we could try to explain the failure of the genetic and epigenetic approaches to factors as diverse as small samples, questionable reliability and validity of measurements, medication confounds, failure to distinguish state and trait effects, correlation–causation ambiguity or, even, false data (Cariaga-Martinez and Alelu-Paz 2016, Mathalon and Ford 2012), but in our opinion, the lack of a theoretical framework that includes and relates clinical, psychological, social and biological variables could explain the sterile accumulation of data in the last years. Although several genes have been implicated and various susceptibility loci for the disorder such as RELN, PLXNA2, ZNF804A or NRG1 (Edwards et al. 2016, Mah et al. 2006, O’Donovan et al. 2008, Shifman et al. 2008), to date, no candidate gene has been conclusively linked to schizophrenia (Alelu-Paz et al. 2016, Cariaga-Martinez et al. 2016, Pearlson and Folley 2008), explaining only a small fraction of the total amount of genetic variation assumed to underlie the disorder and never replicated across populations (Ng et al. 2009, van Dongen and Boomsma 2013). The same could be said for endophenotype analysis (Gottesman and Gould 2003, Owen et al. 2005, Hosák and Hosakova 2015), quantitative trait loci approach (Cariaga-Martinez et al. 2016, Kim et al. 2014, Cariaga-Martinez and Alelu-Paz 2017) and structural and functional studies. In relation to the latter, although several macroscopic findings have been described, some of them presented as major ones, up to now, it is not possible to ensure that there is a clear neuropathological signature for the disorder (Cariaga-Martinez et al. 2016, Harrison and Weinberger 2004); moreover, the positive results in this regard are considered as incomplete, inconsistent, contradictory, non-significant and nonspecific (Harrison and Weinberger 2004).

Do these results imply that we must abandon the neurobiological approach in the study of schizophrenia? The answer is, clearly, no. We think we must reformulate our ideas to understand what schizophrenia is. In this regard, evolutionary approaches represent an interesting theoretical framework to face the paradox that accompanies the disorder.

**Is there an evolutionary framework for schizophrenia?**

We can establish two main classical explanations about the genetic etiology of schizophrenia: the presence of a single, partially dominant gene with low penetrance translated into slight physiological advantages (Srinivasan et al. 2016, Huxley et al. 1964) or many susceptibility genes each one with a small individual effect, which can aggregate by chance to constitute increased risk (Pearlson and Folley 2008, Cannon 2005). Recently, it has been proposed that schizophrenia is the result of human polygenic adaptation, including genes such as DPYD, ZNF804A, NRXN1, NRG3 or VRK2, among others (Srinivasan et al. 2016). None of them have been able to find consistent results, so it is necessary to rethink new strategies to face the problem. In this respect, what does evolution have to say?
Schizophrenia represents an evolutionary paradox: genetic variants that cause predisposition to the disorder persist in the population, despite the fitness reduction in affected individuals (van Dongen and Boomsma 2013). Its evolutionary origins are, up to date, mysterious (Pearlson and Folley 2008) although the literature has provided a host of evolutionary hypotheses trying to clarify the enigma (Polimeni and Reiss 2003). Briefly, these proposals range from those that focus on the survival advantage of heterozygous gene carriers (Brune 2004, Huxley et al. 1964, Erlenmeyer-Kimling 1968, Carter and Watts 1971), through to others that concentrate on the impaired ontogenetic neurodevelopment in the disorder (Brune 2004, Randall 1983, Saugstad 1989, Burns 2004), finishing with those that suggest that schizophrenia represents a trade-off of the evolution of human sociality (Crow 1995b, Brune 2004, Kuttner et al. 1967, Crow 1995a, Stevens and Price 1996). The common denominator to all of them is to consider that the disorder does not represent any evolutionary advantage for our species.

According to Brüne, all of these evolutionary-based explanations are informative only if they account for plausible mechanisms for the preservation of “schizophrenic genes” in the global human genepool, explain the potential sex differences and the heterogeneous symptomatology of the disorder and are consistent with the neuropsychological, developmental and evolutionary findings regarding the human brain (Brune 2004). We think we must add other core facts related to clinical and social aspects, such as the age of onset of the disorder, the absence of structural, biochemical or molecular correlations, the presence of cognitive alterations in all patients and the evidence of a reduced fecundity and increased mortality compared to healthy individuals.

Here we propose a new evolutionary explanation of schizophrenia which aims to conciliate the data now available that may serve as a useful framework for research.

The core facts of schizophrenia

It is evident that genetic variants associated with reduced fitness should be under negative selection pressure, but natural selection has not eliminated them. According to the core facts pointed out before, we need to explain, at least, the following replicated findings present in different dimensions:

From a clinical point of view, the age at onset of schizophrenia, that can be defined in different ways, including age at first admission, age at first positive symptoms and age at first contact with healthcare professionals (Immonen et al. 2017). The data available indicates that the mean age of onset was 21.44 years (SD 8.07) with an earlier age at onset in males (Hare et al. 2010, Eranti et al. 2013), although these results are not consistent when the schizophrenia spectrum disorder diagnosis is included Talonen et al. 2017. Secondly, the cognitive impairment, which is heterogeneity and moderately to severely impaired in patients with schizophrenia, representing the prime driver of the significant disabilities in occupational, social, and economic functioning in these patients affecting attention, memory, reasoning, social cognition and processing speed (Elvevag and Goldberg 2000, van Os et al. 2010, Akbarian 2014, Harvey 2013). The heterogeneous symptomatology of the disorder could be due to methodological problems (i.e. small
samples or unclear clinical histories) (Fioravanti et al. 2005), the clinical diversity of patients included in the studies or, finally, the statistical analysis performed (Fioravanti et al. 2012).

Related to neurobiology, the core fact related to schizophrenia is the absence of reproducibility. As we have suggested, there are many contradictory results that make it impossible to establish a structural, biochemical or molecular pathognomonic pattern of the disease (Maj 2011, Cariaga-Martinez et al. 2016, Cariaga-Martinez and Alelu-Paz 2016, Chua and McKenna 1995, Thune et al. 2001, Keshavan et al. 2011, Shepherd et al. 2012, Dorph-Petersen and Lewis 2017).


Previous evolutionary hypotheses have addressed some of these questions trying to explain the constant incidence rates of the disorder independently of the culture or the environment, despite the fact that, as we have indicated before, people suffering from schizophrenia have a reduced fecundity and an increased risk of mortality compared to the general population (Brune 2004). We could ask ourselves why natural selection maintains susceptibility genes of schizophrenia if the apparent reproductive disadvantage is not compensated for, by any survival advantages; that is, the evolutionary paradox.

**An evolutionary explanation of schizophrenia: shedding light on the enigma**

Our hypothesis suggests that schizophrenia is as a form of brain functioning, among many, that allows us to adapt to the environment and, ultimately, maintain the survival of our species. As Darwin suggested, “variations neither useful nor injurious would not be affected by natural selection and would be left either as a fluctuating element, as perhaps is seen in certain polymorphic species, or would ultimately become fixed, owing to the nature of the organism, and the nature of the conditions…. Due to this struggle, variations, however slight and from whatever proceeding course, if they are to any degree profitable to the individuals of a species, in their infinitely complex relations to other organic beings and to their physical conditions of life, will tend to the preservation of such individuals, and will generally be inherited by the offspring” (Darwin 1859). In other words, the process of natural selection preserves genetic variants associated with survival and reproductive advantage, while genetic variants associated with low fitness are eliminated from the gene pool (van Dongen and Boomsma 2013). This, implies, that individual properties are either favorable, or injurious, or neutral under a certain set of conditions (den Boer 1999).
Explaining schizophrenia as an adaptation to the environment has been the object of significant criticism (Brune 2004, van Dongen and Boomsma 2013, Dubrovsky 2002), suggesting that, although there is an association between schizophrenia and social and musical skills, creativity and intelligence or, even, between schizophrenia and advantageous somatic characteristics (van Dongen and Boomsma 2013), these proposals do not account for the negative effects of this disorder to affected individuals. What's more, we should consider that a trait could be prevalent in a population due to mechanisms such as random mutation, genetic drift or segregation distortion but not for its adaptive advantages (Lane and Luchins 1988). In our opinion, considering schizophrenia as an adaptation to the environment has the same validity and reliability as the hypotheses that consider the disorder as an evolutionary disadvantage. Moreover, the latter have not proposed a theoretical framework that includes the experimental findings obtained to date and are thus limited to the accumulation of data that, as we have said throughout the manuscript, are inconsistent, incoherent and not replicable.

If we consider schizophrenia as an adaptive extreme behavior, can we answer all the questions that remain unknown?

Firstly, we must consider that there is no single way of mind functioning, that is, there is no one way in which our brain faces the environment. The human brain is a highly context-sensitive system, enabling behavioral flexibility in the face of constantly changing environmental challenges (van Os et al. 2010). Schneider already pointed this out several decades ago when he developed his proposal for a clinical psychopathology that described within the general population normal and abnormal psychic reactions to experiences; the latter differ from the first in strength and duration, and included anxiety, depressions, delusions, paranoia, rage and jealousy (Muleh and Carpenter 1973, Schneider 1959). Following this same line, recently, several authors indicate the existence of a subclinical presentation of psychosis, commonly referred to as psychosis proneness, psychotic experiences, schizotypy or at-risk mental states (Siever et al. 1993, Chapman et al. 1994, Claridge 1997, Crow 1998, Kwapil 1998, Verdoux et al. 1998b, van Os et al. 2000, Stefanis et al. 2002, Vollema et al. 2002, Yung et al. 2003, van Os et al. 2009, Verdoux et al. 1998a) that suggests that even though the prevalence of the clinical disorder is low, the prevalence of the symptoms can conceivably be much higher, even when not considered clinically relevant but persistent (van Os et al. 2009, Collip et al. 2013). Therefore, we must admit the existence of a psychosis phenotype expressed along a continuum ranging from attributes widely distributed in the population, ranging from mild subclinical psychotic experiences to full-blown psychotic disorders (Crow 1995b, Schneider 1959, Bebbington 2015, van der Steen et al. 2018) including the daily life stress reactivity as a possible trigger of the disorder in the analysis, since it is considered a marker of sensitization, which in turn has been proposed as the mechanism underlying increased liability to develop persistent psychotic experiences (Collip et al. 2013, Kaymaz et al. 2012).

Therefore, if we understand schizophrenia as an adaptive variation of brain functioning conditioned by the presence of stressful life events, we can explain why natural selection allows schizophrenic genes to persist in the human genome, independently of the decrease in fecundity rates and increase in mortality rates in this population.
Secondly, what about the clinical aspects of the disorder?

Regarding the age at onset of schizophrenia, the results depend, to a great extent, on the diagnostic criteria used, although several studies suggest that there are gender differences in the normal development and maturation of the brain during adolescence, and this period brings about typical gender differences in the epidemiology of mental disorders, including schizophrenia (Talonen et al. 2017, Paus 2010, Paus et al. 2008, Birmaher et al. 2007, Connolly et al. 2007, Fombonne 2009), for example the differences between males and females in their physiological stress response (Bale and Epperson 2015).

However, cognitive impairment is one of the well-recognized characteristics and wide-ranging deficits across all domains of ability in schizophrenia (Neu et al. 2017). The impairments are present before the emergence of positive symptoms and appear stable from the first episode until middle age illness (Davidson et al. 1999, Cornblatt and Erlenmeyer-Kimling 1985, Rund 1998). It is well documented that the cerebral cortex has a key role in cognition (Zola-Morgan and Squire 1993, Goel et al. 1998, Miller 2000, Muller and Knight 2006, Hickok 2009, Apps et al. 2016, Filley and Fields 2016, Lockwood 2016, Millan et al. 2016, Ramirez-Cardenas and Viswanathan 2016, Rosenthal and Soto 2016, Eichenbaum 2017) so we would expect a significant structural impairment in the cortex of schizophrenic patients. However, the results obtained are contradictory, inconsistent and controversial (Weinberger and Berman 1998, Harrison 1999, Manoach 2003, Sayo et al. 2012), thus allowing us to conclude that schizophrenia is characterized by a lack of a unifying neuropathology (Cariaga-Martinez et al. 2016, Catts et al. 2013, Dorph-Petersen and Lewis 2011), at least as far as the cerebral cortex is concerned.

So, how can we explain this cognitive impairment without significant structural impairment in the cerebral cortex of schizophrenic patients? Should we go beyond the cortex?

Let's focus on a subcortical structure where further knowledge has modified our traditional view of how the brain processes information: the thalamus.

This evolutionary conserved structure has extensive reciprocal connections to cortical regions (Nakajima and Halassa 2017). It is located near the middle of the brain and it can be divided into dorsal and ventral divisions related to embryonic origin (Sherman 2017), being involved in a wide range of cognitive, sensorymotor and limbic functions acting as a gate or a high pass filter which represents a bottleneck for the transfer of information to cortex in an efficient way (Sherman 2017, Alelu-Paz and Gimenez-Amaya 2008, Connelly et al. 2015). Moreover, several authors suggest that its function cannot be dissociated from that of the cortex in attention, perception, consciousness or the integration of thought processes (Jones 1997, Penner et al. 2018), that is, those that are impaired in schizophrenia.

We suggest that the thalamus acts as a gate: by gating we refer the fact that one type of thalamic cell- relay cells- receive strong inhibitory GABAergic inputs from local and external sources; if these inputs are very active, the gate is shut and there is no relay to cortex, if the inputs are silent, the gate is open, and if the inputs are moderately active, the gate is...

As a first approach, it can be hypothesized that a structural impairment in the thalamus (i.e. volume, total cell number), could underlay the cognitive deficit characteristic of schizophrenia, according to its function as a mediator between the external world and the cerebral cortex controlling the flow of information from below to top (Sherman 2017) or, even, due to its role in natural recovery of cognitive impairment after brain injury (Munivenkatappa et al. 2016), but the data available up to now is inconsistent and contradictory (Dorph-Petersen and Lewis 2017) and, therefore, it is mandatory to discard this possibility.

However, what can be said about function? Beyond the structure, recent studies suggest an altered thalamo-cortical pattern of connectivity in schizophrenia which translate into an increased thalamic connectivity with all sensory-motor cortices (Anticevic et al. 2014) and a reduced total connectivity with orbitofrontal cortex, prefrontal cortex, striatum, anterior cingulate cortex, cerebellum, parahippocampal gyrus and inferior parietal cortex (Anticevic et al. 2014, Marenco et al. 2012, Cho et al. 2016, Giraldo-Chica et al. 2018, Hamoda et al. 2018, Zaytseva et al. 2018), being present this aberrant thalamo-cortical connectivity in the early stages of the disorder (Hamoda et al. 2018) and, in some cases, related to symptoms that are characteristic of schizophrenia (Zaytseva et al. 2018, Li et al. 2017).

We hypothesized that this aberrant thalamo-cortical connectivity is a consequence of the presence of stressful life events and, more specifically, we suggest that the management of these events by the thalamus fails due to the shutdown of interneurons, with the corresponding absence of control of the flow of information to cortex. The latter, the cortex, as a physical system, would not be able to manage the information without the thalamus functioning correctly, hence the appearance of alterations in the processing of information that result in the cognitive alterations that are characteristic of the disorder.

The consequence of the aforementioned hypothesis is evident: the clinical picture of schizophrenia is the trade-off that some individuals pay for adapting to the environment.

**Moving beyond theory: an experimental proposal**

How can we check the theory proposed? As we previously pointed out, our theory accounts for plausible mechanisms for the preservation of “schizophrenic genes” in the global human genepool, explaining the heterogeneous cognitive symptomatology of the
disorder, and is consistent with the neuropsychological, developmental and evolutionary findings regarding the human brain, at least with those that are consistently linked to the disorder. Moreover, it provides an answer to the questions posed by the different epidemiological studies on schizophrenia.

Regardless, beyond the theory, we think it necessary to provide an experimental approach that allows us to refute what we propose here.

Due to the fact that we consider the thalamic interneurons as the main actor that, in the presence of certain stressful events of daily life, stop working correctly, altering thalamo-cortical connectivity patterns, we think we need to focus on the epigenetic signatures that are specific to each cell population and, more specifically, of those genes involved in the interneuron functioning, such as SLITRK3 or PTPRD, both regulating the number of functional inhibitory synapses (Takahashi et al. 2012). We would expect, as null hypothesis, a non-altered epigenetic pattern (DNA methylation or histone modifications) of these genes in schizophrenic interneurons compared to healthy interneurons. We focus on epigenetics because the stress-vulnerability model of etiology assumes that genetic factors operate by making individuals selectively vulnerable to environmental risks. Accordingly, epigenetics refers to the interplay between environment and genes that initiate and maintain heritable patterns of gene expression and function without changing the sequence of the genome (Urdinguio et al. 2009). It is considered that epigenetic processes are highly dynamic even within an individual, being involved in the regulation of many developmental processes including the programs of gene expression that result in the development of different organs, tissues (Shipony et al. 2014) and, even, among different subpopulations of a given cell type (Iwamoto et al. 2011, Kozlenkov et al. 2014, Kozlenkov et al. 2016), i.e. interneurons and projection neurons. Therefore, we can conclude that these specific epigenetic markers may help to explain brain region-specific and cell type-specific differences in gene transcription, and are critical in order to analyze the degree to which brain epigenetic signatures might be altered in severe mental diseases, such as schizophrenia (Ladd-Acosta et al. 2007).

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Author contributions

APR conceive the manuscript and CMA, GKJ and APR wrote the manuscript.
Conflicts of interest

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References


persistence of psychotic experiences in a longitudinal general population study. PLOS One 8 (4): e62688. https://doi.org/10.1371/journal.pone.0062688


- Dorph-Petersen KA, Lewis DA (2017) Postmortem structural studies of the thalamus in schizophrenia. Schizophrenia Research 180: 28-35. https://doi.org/10.1016/j.schres.2016.08.007


Power RA, Kyaga S, Uher R, MacCabe JH, Langstrom N, Landen M, McGuinff P, Lewis CM, Lichtenstein P, Svensson AC (2013) Fecundity of patients with schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, or substance abuse vs their...


