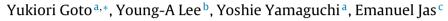
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# Biological mechanisms underlying evolutionary origins of psychotic and mood disorders



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#### ABSTRACT

Psychotic and mood disorders are brain dysfunctions that are caused by gene environment interactions. Although these disorders are disadvantageous and involve behavioral phenotypes that decrease the reproductive success of afflicted individuals in the modern human society, the prevalence of these disorders have remained constant in the population. Here, we propose several biological mechanisms by which the genes associated with psychotic and mood disorders could be selected for in specific environmental conditions that provide evolutionary bases for explanations of when, why, and where these disorders emerged and have been maintained in humans. We discuss the evolutionary origins of psychotic and mood disorders with specific focuses on the roles of dopamine and serotonin in the conditions of social competitiveness/hierarchy and maternal care and other potential mechanisms, such as social network homophily and symbiosis.

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#### 1. Introduction

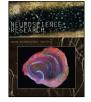
Psychotic and mood disorders such as schizophrenia (SCZ) and major depressive disorder (MDD) are devastating mental problems

with symptoms that include cognitive dysfunction and affective disturbance. Epidemiological studies have reported that the fecundity rates of subjects with psychotic and mood disorders are significantly lower than those of normal subjects (Power et al., 2013), which suggests that the symptoms of these disorders are disadvantageous behavioral phenotypes, at least in modern human society. Nevertheless, psychotic and mood disorders have been present at constant incidences in humans since an ancient era (Berrios, 1988; Kyziridis, 2005). A major question is why psychotic

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Perspective



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and mood disorders emerged and have been maintained at a constant prevalence in humans despite natural selection, which predicts the elimination of phenotypes that do not match the environment.

By drawing evidence together from a range of published research, we present mechanisms of gene–environment interactions that may have played roles in the selection and maintenance of alleles that increase the risks of psychotic and mood disorders in evolution. We discuss this issue with a specific focus on the roles of dopamine (DA) and serotonin (5-HT) transmission in (1) social competitiveness/hierarchy, (2) maternal care, (3) social network homophily, and (4) symbiosis.

## 2. Positive selection of genes associated with psychotic and mood disorders

Genetic factors play roles in psychotic and mood disorders. The heritability rates of psychiatric disorders, including psychotic and mood disorders, are estimated to be approximately 0.4–0.8 depending on the type of disorders (Eaton et al., 2008; Sullivan et al., 2012). Several genetic mechanisms may answer the questions of how and why disadvantageous alleles that increase the risks of psychotic and mood disorders have been selected for and maintained despite natural selection in evolution. These potential mechanisms are not mutually exclusive and are intermingled in terms of the causes of disorders.

One possible explanation is that de novo mutations of genes occur rarely but yield large effects (Gratten et al., 2014; Malhotra and Sebat, 2012; Sullivan et al., 2012). Because de novo mutations may occur at a constant rate, such mutation could explain the constant prevalence of psychotic and mood disorders even given the decreased fecundity of patients (Malhotra and Sebat, 2012). Sporadic cases of SCZ and autism spectrum disorder (ASD) with no family histories have been reported (Cuccaro et al., 2003; Lewis et al., 1987; Roy and Crowe, 1994), and de novo mutations may play significant roles in such cases. However, because the frequency of de novo mutations is extremely low, it is estimated that only a fraction of cases at most can be explained by de novo mutations (Gratten et al., 2014; Malhotra and Sebat, 2012; Sullivan et al., 2012). Thus, other mechanisms should also be involved.

The neutral selection of genes (Kimura, 1968; Kimura and Ohta, 1971) is another possible explanation. The effect of each allele associated with psychotic and mood disorders is too small to yield either an advantageous or disadvantageous influence, and the allele consequently escapes the selection process. However, when these alleles with small effects are combined, symptomatic conditions may emerge. Common genetic variants with small effect sizes that increase the risks (odds ratios) of psychiatric disorders, including psychotic and mood disorders, by approximately 1.05–1.2 at most have been identified (Gratten et al., 2014). Such common alleles are estimated to account for 30–50% of cases due to the accumulated contributions of multiple alleles (Gratten et al., 2014). Ripke and colleagues estimated that 50% of SCZ cases could be explained by 8332 single nucleotide polymorphisms (SNPs) (Ripke et al., 2013).

An alternative explanation depends on the notion that an allele or a set of alleles associated with psychotic and mood disorders yield small but significant effects that are disadvantageous and thereby subjected to natural selection; however, such disadvantageous phenotypes are maintained by balancing selection because they can also function advantageously in specific environmental conditions.

Explorations of the evolutionary origins of human diseases have been attempted in the field of evolutionary medicine (Gluckman et al., 2011). Evolutionary medicine is distinct from conventional biomedical research in that it emphasizes the understanding of "why" rather than "how" diseases are caused. Trade-offs in biological function during evolution are thought to be involved in many human diseases. For example, erect bipedalism enabled free hand use in hominids, but the trade-offs include diseases such as thrombophlebitis and herniated lumber vertebral disks (Haeusler et al., 2013). The loss of urase oxidase activity in several species, including humans and non-human primates, resulted in prolonged longevity due to the anti-oxidant effects of uric acid; however, the accumulation of uric acid also causes gouty arthritis (Johnson et al., 2009).

Environments are critical determinants of the selection of genetic variants based on the behavioral phenotypes that result from mutations. The sickle cell trait is caused by nonsynonymous mutations of the  $\beta$ -globin gene that result in amino acid sequence changes that alter red blood cell structure and function (Rees et al., 2010). Sickle cell disease occurs in various types that are determined by the parts of the  $\beta$ -globin in which the mutations occur (Rees et al., 2010). The most common mutation is caused by an  $A \rightarrow T$  SNP that results in the replacement of glutamic acid with valine (Rees et al., 2010). Sickle cell mutation homozygosity is often lethal, and heterozygotes suffer from disadvantageous phenotypes that include anemia. Nevertheless, a high prevalence of this genotype has been maintained in malaria epidemic regions in Africa, because this genotype confers resistance to malaria infection (Beutler et al., 1955). Thus, specific environmental factors can preserve genotypes associated with diseases that are disadvantageous in normal conditions.

Whether psychotic and mood disorders involve balancing selection forces similar to those that affect sickle cells remains unknown. Nevertheless, because environmental risk factors such as stress play significant roles in most if not all psychotic and mood disorders (Burt, 2009; Hammen, 2005; Lewis and Levitt, 2002; Rabkin, 1980; Schmitt et al., 2014), the mechanisms that sufficiently explain the causes of psychotic and mood disorders should be considered within the framework of gene-environment interactions with or without epigenetic mechanism and not in the framework of genetic variants alone.

## 3. Are psychotic and mood disorders uniquely nested in human evolution?

A study by Crespi et al. (2007) demonstrated that traces of positive selection, selective sweep (i.e., reductions in genetic variations in the vicinity of variants under positive selection due to hitch-hiking effects among population (Nielsen et al., 2007)) and the dN/dS ratio (i.e., the ratio of non-synonymous to synonymous variants (Kimura, 1977)) are found approximately twice more frequently among SCZ candidate genes than other control genes (i.e., those associated with neuronal activity). Additionally, a study by Ogawa and Vallender revealed that the dN/dS ratios of the genes that are homologous to SCZ and ASD candidate genes are significantly higher in catarrhini (old world monkeys, anthropoids, and humans) and cetacea (dolphins and whales) than other species of animals, which suggests that the alleles associated with SCZ and ASD have been subjected to positive selection and have played important roles in the evolutions of the brains of species such as catarrhini and cetacea with brain sizes that are larger than those of other species (Ogawa and Vallender, 2014). If such alleles are involved in the expansion of the size of the brain, this finding would explain how catarrhine primates and cetaceans acquired superior social intelligence.

Whether psychotic and mood disorders are unique human conditions that are not present in other animals essentially remains unknown because no systematic research has been conducted to answer this question. However, behavioral manifestations that are Download English Version:

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