What´s in a Trait? Reconceptualizing Neurodevelopmental Timing by Seizing Insights from Philosophy and EvoDevo

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Abstract

Philosophy has long been debated for its relevance to natural sciences. Drawing from evolutionary biology, I exemplify how philosophy contributed to scientific discourse, in particular to the concept of genes and traits. Rather than determining distinct traits, genes influence the plastic development of traits, especially during sensitive periods. EvoDevo further integrates philosophical insights to explore how developmental processes influence evolutionary change. I highlight the concept of heterochrony which describes temporal changes of developmental events during evolution. I argue that neuroscience could also benefit from similar conceptual scrutiny. In the paper, I discuss the expansion of the human neocortex in light of heterochrony and developmental plasticity as a key example. Plasticity allows organisms to adapt to fluctuating environments characteristic of the human cognitive niche and contributes to diversity. As an effect of heterochrony, postnatal brain development in modern humans is prolonged and the brain remains highly plastic. While periods of plasticity enable developmental variability, they also introduce the risk of neurodevelopmental aberrations, such as in schizophrenia. Schizophrenia is characterized by an abnormal prolongation of neuroplasticity due to an impaired excitatory/inhibitory balance and excessive synaptic pruning, particularly in the prefrontal cortex. This "overpruning" combined with delayed maturation may contribute to the disorder´s onset and progression. The interplay between environmental factors and neurodevelopment during sensitive periods is crucial in shaping the disease outcome. This reconceptualization challenges traditional gene-for-trait paradigms and instead advocates for a focus on developmental timing during different life stages to better understand the etiology of psychopathologies and potential intervention strategies.

Introduction – a shift in the concept of genes

There is a running joke among natural scientists that "philosophy of science is about as useful to scientists as ornithology is to birds11This quote is frequently attributed to Richard Feynman, although there is no verifiable source or record of Feynman actually saying this exact phrase." (Kitcher, 1998; p. 32). Why should neuroscientists grapple with philosophy? Can philosophy inform neuroscience in any useful way? To unpack this question, let us look at the more recent scientific history to evaluate how philosophy has previously contributed to biological debates.

To this end, I want to use the example of evolutionary biology and its relation to philosophy of biology. In the mid-20th century, the discovery of the double helix and the elucidation of the genetic code revolutionized biology and raised profound philosophical questions about the nature of genetic information, heredity, and biological causation. These key developments prompted philosophical reflections on reductionism, determinism, and the relationship between genes and phenotypes. Around the same time, the "hardening" of the Modern Synthesis22The Modern Synthesis refers to the synthesis of Charles Darwin's theory of evolution and Gregor Mendel's concepts of heredity into a joint mathematical framework (Huxley, 1942). proceeded (Gould, 1983) integrating Mendelian genetics, Darwinian evolutionary theory, and molecular biology. The Modern Synthesis kindled philosophical discussions about the nature of genes, selection, adaptation, and the relationship between genetics and evolution.

A key concept that underwent significant philosophical scrutiny over time was the notion of the gene. Initially, genes were viewed as units of heredity. With the advent of molecular genetics in the mid-20$^{\text{th}}$ century, genes were defined as stretches of DNA that encode specific sequences of nucleotides, which in turn specify the sequences of amino acids in proteins. In other words, genes were conceptualized in a narrow sense, as the open reading frame on the DNA from the start of translation to the respective stop codon (Watson, 1970). The definition of a gene was later expanded to include introns; the 5' and 3' UTRs (untranslated regions); regulatory elements, such as promoters, transcription enhancers, and silencers; and eventually also noncoding RNAs (i.e., "non-protein-coding RNAs"33Non-protein-coding RNAs are usually are encoded and transcribed by their own genes (Brosius, 2009)).

The shift in understanding what constitutes a gene was paralleled by another conceptual issue that referred to the biological function of a gene. Initially, biologists talked about genes "*for* " a particular trait or function (Keller, 2000). In classical genetics in the early 20$^{\text{th}}$ century, the terminology in use entrenched the notion of a gene "*for* " a particular trait and implied a direct, one-to-one relationship between genes and phenotypic traits. This corroborated the assumption that there would be a gene "*for* " eye color or a gene "*for* " height, and so on. As research progressed, it became clear that the relationship between genes and phenotypic traits is often more complex than a simple one-to-one correspondence. Many traits are influenced by multiple genes (polygenic effects), as well as environmental factors and gene-environment interactions. Additionally, genes can have pleiotropic effects, i.e., a single gene can influence multiple traits.

What makes a trait?

For the longest time throughout the 20$^{\text{th}}$ century, the concept of a gene followed the conventional paradigm described above. This stance suggested that genes exert their effects unidirectionally (i.e., from DNA to mRNA to protein to phenotypic trait) and code for particular traits in a one-to-one manner. Based on these premises, many research programs were devoted to finding genes that coded "*for* " a particular trait. These research agendas included complex traits such as morphological, physiological, and behavioral characteristics.

However, the notion of a gene "*for* " a particular trait has turned out to be far too narrow. This predicament was not missed by philosophers of biology (Moss, 2004). Contemporary biologists acknowledge that the relationship between genes and phenotypes is much more complex and multifaceted than previously suggested. This way of non-reductionist, context-dependent thinking represents a significant shift from a gene-centric view to an organism-centric view that includes the embedding of the organism in its specific niche (Odling-Smee*et al* ., 2003). The epistemic shift occurred gradually over several decades and was influenced by empirical discoveries, theoretical advances, and, not least, conceptual contributions from philosophers of biology (Jablonka & Lamb, 2005; Godfrey-Smith, 1996; Sterelny, 2003). Key insights that fueled this epistemic shift came from the novel field of evolutionary developmental biology (EvoDevo) that emphasized the complex interactions between genes, regulatory elements, and the environment, highlighting the importance of gene regulation, epigenetics, and gene-environment interactions in shaping phenotypic variation. In the meantime, in other fields of biology, the notion of a gene "*for* " matured into the notion of a gene "*involved in.* " Yet, the latter hardly provided any more explanations of how genes contributed to the genesis of traits.

In its traditional definition, a trait is a specific characteristic or feature of an organism that can be inherited, observed, and measured. Research questions have largely focused on explaining the inheritance of a phenotypic trait, but without explaining how that trait develops. This confusion is rooted in the standard theory of evolution, the Modern Synthesis, that grants genetic information the role of a deterministic program to be executed or an instruction to be followed (Laland *et al* ., 2014). However, the development of phenotypic traits is governed not so much by nucleotide sequences as by spatiotemporal patterns of gene expression—that are part of complex interaction networks and are subject to intrinsic and extrinsic stimuli (internal and external to the cell, respectively)—as well as by epigenetic modifications and distinct DNA conformations.

A thought-provoking conceptual understanding about how genes contribute to the phenotypic emergence of traits comes from EvoDevo rooted in collaborative work by theoretical biologists and philosophers of biology (Sultan, *et al* ., 2022). According to EvoDevo researchers, traits are characterized as the outcome

of developmental processes to which genes and their products contribute important interactants (Moczek, 2020). Besides genes and gene products, other factors and processes play equally important roles in the formation of traits, such as cell-cell signaling, or reciprocal induction of tissues, or complex feedback loops among components of organ system (Moczek 2015a). Naturally, genes and their allelic variations contribute to these processes that take place on various levels of biological organization, ensuring high predictability and reliability of these interactions by intergenerational, heritable transmission. However, when looking on the organismal level, the role that genes play is significantly more complex, versatile, and non-linear than when looking at their roles on the molecular level. EvoDevo biologist Armin Moczek urges that research requires "a reorientation away from an understanding of traits and organisms as residing solely in genes and genomes, and toward an appreciation of traits as products of developmental systems" (Moczek, 2020; p. 76).

Philosopher Evelyn Fox Keller convincingly argues along the same lines. "[R]ecognizing that, however crucial the role of DNA in development and evolution, by itself, DNA doesn't do anything. It does not make a trait; it does not even encode a program for development. Rather, it is more accurate to think of DNA as a standing resource on which a cell can draw for survival and reproduction, a resource it can deploy in many different ways, a resource so rich as to enable the cell to respond to its changing environment with immense subtlety and variety. As a resource, DNA is indispensable; it can even be said to be a primary resource. But a cell's DNA is always and necessarily embedded in an immensely complex and entangled system of interacting resources that are, collectively, what give rise to the development of traits" (Keller, 2010; p. 51).

Other important insights that challenge the gene-centric view and the notion of a-gene-"*for* "-a-particular-trait come from studies of phenotypic plasticity. Phenotypic plasticity is the ability of organisms to produce different phenotypes in response to environmental cues. This phenomenon of plasticity is diametrically opposed to the idea of "fixed" traits. Rather than being static, fixed characteristics, traits unfold over time during the organism´s lifespan and in relation to the organism´s niche. Hence, trait development is seen as the result of interactions between genotypes and complex non-genetic environments as well as of epistatic interactions between genes. The manifestation of a given trait strongly depends on an organism´s capacity of plasticity. To quote evolutionary biologist Armin Moczek, "[w]ithout explicit consideration of plasticity, our understanding of any trait, any pattern of variation within a population, and any reconstruction or prediction of evolutionary trajectories would be incomplete" (Moczek, 2015b; p. 302). Plasticity is a hallmark of development. It enables species to cope with environmental heterogeneity and allows organisms to adaptively (and sometimes also non-adaptively) adjust their phenotype within a range set by genetic and developmental constraints thereby coping with variability in the conditions of the environment. In this sense, plasticity is a bedrock capacity for a trait to come into being. This dynamic view on traits expound that traits exhibit significant variations at different life stages and under different environmental conditions. Analogously, plasticity gains increasing significance for organisms in environments that do not exert a stable, but a fluctuating pressure on them. This is clearly the case for long-living species such as humans that occupy a panoply of niches and can move between them.

A matter of timing

EvoDevo emerged as a new research field that is interested in how changes in organismal development relate to evolutionary changes that span over many generations (Hall, 2012; Hendrikse *et al* ., 2007). For example, EvoDevo scientists aim at identifying and explaining the specific developmental events that lead to the evolution of new traits and body plans generating morphological diversity (Wilkins, 2002). Focusing on developmental processes of whole organisms rather than just biochemical and cellular processes, scientists scrutinize reductionist views such as the one-to-one correlations between genotype and phenotype and the concept of a gene-"*for* "-a-particular-trait. Going beyond mechanistic, genetic explanations for complex traits and behaviors by solely breaking them down into their constituent parts, scientists now look at processes on the level of the whole organism. One of the most surprising insights from EvoDevo is observation that many fundamental aspects of development are quite conserved across diverse organisms. Many key developmental pathways and mechanisms are shared among distantly related species, from simple organisms like fruit flies and nematodes to more complex organisms like vertebrates and plants. For example, the genetic toolkit

responsible for body plan formation is highly conserved, indicating ancient origins and widespread utility across different taxa. Genes involved in building specific body parts and organs in the fruit fly have functional equivalents in humans (Carroll, 2017). Based on more and more findings supporting the idea of highly conserved key regulators of development, researchers postulated that important differences among organisms are not due to the presence and absence of genes. "Instead, much of the phenotypic diversity we see is due to changes in the regulation of expression in time and space of these highly conserved genes" (Smith, 2003, p. 616). Such processes include alterations in the timing or duration of developmental processes that can produce phenotypic differences. Along these lines, Barbara McClintock famously stated, "[i]f I could control the time of gene action, I could cause a fertilized snail egg to develop into an elephant. Their biochemistries are not all that different; it's simply a matter of timing" (cited after West-Eberhard, 2003).

Temporal alterations concern changes in the timing of regulatory pathways or the timing of gene activation during development. The expression of traits may even be shifted from one life stage to another, a phenomenon that has been termed heterochrony (Smith, 2003; McKinney & McNamara, 1991; Reilly *et al* ., 1997). Some researchers go as far as saying that "all developmental events occur along a time line, any significant change is likely to result in a heterochrony at some level" (Raff, 1992, p. 211). The umbrella term of heterochrony comprises acceleration (precocious development) or retardation (delayed development) of specific developmental processes, relative to the ancestral condition (McKinney & McNamara, 1991) or relative to homologous processes in other taxa (Smith, 2003). A regulatory shift in the timing or duration of developmental processes can produce significant phenotypic differences between individuals or species that allow for the emergence of novel phenotypes and contribute to evolutionary diversification (Shubin *et al* ., 1997; West-Eberhard, 2003). Advances in EvoDevo were significantly enriched by philosophers who gave critical assessments of the conceptual, theoretical, and methodological foundations of the field. By employing philosophical analyses, biologists have come to a richer understanding of the complexities of development and evolution. The scrutinized definition of what a gene *is* helped in conceptualizing what genes can and cannot "do" in an organism (Moss, 2004) as well as which roles they play in development and evolution. Furthermore, the shift in focus from individual genes to development as a system that integrates genetic, environmental, and epigenetic factors (Oyama, 2000) contributed to the formulation of an extended evolutionary theory, i.e., the Extended Evolutionary Synthesis (Müller & Pigliucci, 2010).

Drawing on experiences from the interdisciplinary endeavors in EvoDevo, the question arises whether neuroscience can also benefit from philosophical analyses, in a similar manner as EvoDevo did. I will argue in favor of using a philosophical approach of conceptual inquiry to be adopted by neuroscience. I will substantiate this claim by means of two examples: first the expansion of the neocortex in hominid evolution and second how schizophrenia can be reconceptualized as a disorder of sensitive periods enabled by heterochronic shifts in brain development.

The case of cortex expansion in hominid evolution

EvoDevo acknowledges that major innovations in evolution involve extensive alteration processes that go beyond small genetic changes and gradual accumulation of mutations11EvoDevo researchers identified five main mechanisms that are involved in the generation of anatomical diversity through changes in development: - change in developmental timing (heterochrony) - change in developmental location/spatial expression (heterotopy) - changing the sequence of genes being expressed during development (heterotypy) - change in the amount of developmental product (heterometry) - change in the governance of a trait from being environmentally induced to being genetically fixed (heterocyberny). For example, evolutionary novelties, such as complex structures or novel organs that are not present in ancestral groups, may be the result of changes in developmental timing (i.e., heterochrony). These changes may have been enabled by either large-scale genetic alterations or by co-option of existing genetic pathways for new functions. It has been argued that mutations in regulatory regions that effect the spatial and temporal expression of whole networks significantly contribute to discontinuous changes in phenotypic variation and effect the likelihood of trait retention and its spread in a population (Carroll, 2008). As argued above, most genes do not code "*for* " a single trait but have pleiotropic effects prompting them for co-option or gene recruitment. Similarly,

many phenotypic traits have not evolved exerting a single, distinct feature, but they can be co-opted over evolutionary time to respond to new challenges. Thus, traits can be exploited in new contexts or remodeled during ontogenesis. Such processes are termed exaptations, rather than adaptations (Gould & Vrba, 1982). Exaptations play an important role in the evolution of cognitive features in humans. In fact, paleontologists Gould and Vrba claimed that "[m]ost of what the brain now does to enhance our survival lies in the domain of exaptation" (Gould & Vrba, 1982; p. 13). Conclusive examples of such exaptations are the human-specific capacities of reading and arithmetic that recruit phylogenetically conserved neuronal precursors. Dehaene has termed the neuroplastic process of exaptation that is characterized by co-opting existing brain circuits for the acquisitions of novel cultural operations the "neuronal recycling hypothesis" (Dehane, 2005).

Evolutionary novelties resulting from discontinuous changes of traits are usually the result of extensive rearrangement processes. The rearrangement can be driven by gene duplication, regulatory rewiring, or genetic recombination. Gene duplication produces additional copies of genes allowing one copy to retain the original function while the other can undergo evolutionary modification and thereby providing the potential for novel functions. This is what may drive evolutionary innovation through the acquisition of new features or adaptations that enhance the fitness of organisms in their environment. For example, innovations (i.e., successful novelties) can facilitate new modes of locomotion, sensory organs, feeding strategies, or reproductive strategies, allowing individuals of a population to exploit new ecological niches or more flexibly respond to changing environmental conditions. In the most successful cases, phenotypic novelties can trigger adaptive radiation by opening up new ecological opportunities thereby leading to the rapid diversification and speciation of lineages. Examples of such key innovations or adaptive break-throughs are the evolution of flight in birds or insects, the development of flowers in angiosperms, or the origin of jaws in vertebrates.

An eminent evolutionary innovation in the hominin lineage is the expansion of the human neocortex. The cortex expansion of humans has been associated with increased cognitive abilities and behavioral complexity, which are considered key adaptations in human evolution. Higher cognitive functions that involve the neocortex include spatial reasoning, language processing, executive functions, and social cognition. Complex behavior associated with an expanded human cortex paved the way for complex problem-solving abilities, abstract reasoning, the capacity for self-awareness and introspection as well as language, tool use, symbolic thinking, and the capacity of scaffolded cultural transmission. These human-specific, complex skills presumably provided impetus for an increasingly sophisticated, cumulative cultural evolution.

The expansion of the human cortex is likely the result of a reciprocal interplay between genetic, developmental, evolutionary, and environmental factors. A large body of research exists on individual genes and their combined effects that are involved in the evolutionary expansion of the human cortex. These candidate genes have been extensively reviewed elsewhere (Lui *et al* ., 2011; Sousa *et al* ., 2017; Molnar *et al* ., 2019; Franchini, 2021). Clearly, the number of species-specific genes cannot account for differences in functional and behavioral complexity between human and non-human primates (King & Wilson, 1975). Instead, a relatively small number of genetic changes that regulate gene expression in both, humans and chimpanzees, seem to be responsible for the major organismal differences (Richtsmeier, 2018). In particular, changes that affect the timing or spatial distribution of gene expression involved in developmental processes can lead to drastic phenotypic variations and can ultimately result in phyletic changes (Carroll, 2005; Carroll, *et al* ., 2001). In this paper, I will use a specific example to explore changes in developmental timing and argue that heterochronic effects have probably contributed significantly to the expansion of the human cortex.

A key pathway that plays an important role in cortex expansion includes the SRGAP2 (Slit-Robo Rho GTPase Activating Protein 2) gene product. The*SRGAP2* gene regulates neuronal migration and differentiation by inducing filopodia formation, branching of neurons, and neurite outgrowth, modulates synaptic plasticity, and controls the dynamics (e.g., the density and morphology) of dendritic spines. One of the crucial changes that likely underlies the human-specific evolutionary transition leading to the expansion of the neocortex is the duplication of the *SRGAP2* gene. This duplication occurred in the human lineage after the divergence from the common ancestor of humans and chimpanzees. The duplication process gave rise to novel gene variants,*SRGAP2B, SRGAP2C, SRGAP2D* , which exhibit a high sequence identity with little genetic variation

(Dennis *et al.* , 2012).

One of the duplicated genes, *SRGAP2C* , was shown to be biologically active and expressed at high levels. The resulting protein does not contain the full-length sequence of the ancestral gene, but is a truncated version of the original SRGAP2 protein (the latter is named SRGAP2A in humans). The SRGAP2C protein binds to SRGAP2A protein and exerts a dominant negative effect resulting in a significant loss of function of the original SRGAP2 protein. As a result of this functional loss due to oligomerization, pyramidal neurons that express the respective genes, migrate faster and take much longer for their dendritic spines to fully sprout. On the other hand, the delayed growth of spines of pyramidal neurons allows many more spines to be formed at full maturation. Thus, the duplicated *SRGAP2* genes—in concert with other genes—triggered a change in the developmental trajectories and maturation process by influencing the developmental course of neuronal and synaptic morphogenesis (Dennis *et al* ., 2012). The increased migration speed of the cortical neurons on the one hand and the slower maturation of the synaptic spines on the other hand most likely contributed to the expansion of the cortex in the lineage of*Homo sapiens* (Charrier *et al* ., 2012; Guerrier *et al* ., 2009; Guo & Bao, 2010; Sarto-Jackson *et al* ., 2017). These modified cortical maturation processes cannot be observed in chimpanzees, orangutans, and gorillas (Sudmant *et al* ., 2010). Phylogenetic classification analyses confirm that the time frame of incomplete gene duplication of the *SRGAP2* gene correlates with the phylogenetic transition of the genus *Australopithecus* to the genus *Homo* .

In a nutshell, changes in the timing of brain development over the course of evolution led to an increase in the neocortical brain surface (Lui *et al* . 2011; Rakic 2009) that allowed new cognitive skills to emerge, which natural selection could act upon. As a result of the prolonged maturation process, more complex neuronal morphology and increased neuronal connectivity could develop contributing to the complexity and the increased multifunctionality of the neocortex in humans, thus, representing a paradigmatic key innovation in evolution. Noteworthy, by transmitting the duplicated *SRGAP2* gene to the next generation, what gets passed on is not a particular gene "*for* " cortex expansion that determines a unique human "trait of an enlarged brain," but the neuroplastic capacity of a species-typical developmental trajectory. This capacity is realized by a multitude of intertwined, neuroplastic processes that effect developmental timing, most likely in a cascade-like manner.

When plasticity becomes maladaptive

Recognizing that plastic developmental processes are tightly intertwined with evolution, despite them operating on very different time scales, exemplifies the complexity and multidimensionality of evolutionary processes. One way how plasticity can guide evolution, is through niche construction (Odling-Smee *et al.* , 2003). Niche construction denotes the processes how organisms influence the conditions of their own evolutionary trajectories by shaping their environment. While most—if not all—organisms construct their niche to a certain extent, humans represent the most extreme niche constructors. Due to advanced cognitive abilities and complex social behaviors, *Homo sapiens* occupies a unique niche that is referred to as human cognitive niche (Tooby & DeVore, 1987; Pinker, 2010). This niche is characterized by features that distinguish it from niches that other species occupy. For example, humans have evolved sophisticated language capabilities, allowing for complex communication, collaboration, as well as abstract and symbolic thinking. These species-typic abilities have prepared the ground for the development and transmission of cultural practices as well as scientific and technological advancements.

In order to reliably reproduce the unique skills and cognitive capabilities required to succeed in this cognitive niche, humans must undergo an extraordinarily extended period of learning characterized by heightened neuroplasticity. These periods of plasticity are paralleled by a formidable increase in grey matter resulting from postnatal synaptogenesis as well as dendritic and axonal arborization. Prolonged synaptogenesis allows for a massive increase in possible synaptic combinations that allows for extensive synaptic pruning to follow. Unsurprisingly, an exceptionally long maturation process of various brain areas contributes to the large inter-individual variability amongst humans. This aligns well with the observation that in mammalian phylogeny from rodents to primates, there is a continuous increase in inter-individual differences concerning the densities of synapses, the amounts of neurotransmitters, and the metabolic activities of cortical areas (Bourgeois, 1997).

Naturally, such differences conferred by plasticity are the substrate that natural selection can work upon.

A prolonged maturation process that is accompanied by long-lasting neuroplasticity also increases the vulnerability of the brain if exposed to adverse environments (Sarto-Jackson, 2022). Since a significant proportion of brain maturation processes occurs outside of the maternal womb, "unbuffered" environmental influences can drastically impact the infant´s developmental trajectories. With the largely unfettered influence of the environment, synapses and neural circuits are subject to a rigorous selection process in the course of ontogeny through idiosyncratic experiences and learning processes. Due to a tremendous increase in the variability of environmental conditions in the human niche (e.g., changes in the cultural, technological, and virtual environment), modern humans may currently experience an excess of developmental variations of cognitive and social skills. This is in agreement with the observation from a wide range of species showing that after the emergence of novelties (such as the expansion of the human neocortex), there is at first a rapid diversification that gradually slows down later as the lineages of the species evolve (Uller *et al* ., 2018). Importantly, such excessive variation based on plasticity are not necessarily adaptive, but can include maladaptive responses (Parsons *et al.* , 2020). This is an important phenomenon that might contribute to the emergence of psychopathologies in individuals living in modern societies.

A psychopathology that may have emerged in the human population fostered by extensive developmental variabilities within the human socio-cultural niche is schizophrenia. It is an intriguing evolutionary paradox that a debilitating psychiatric disease like schizophrenia persist in human populations despite its negative impact on reproductive fitness (Hunt & Jaeggi, 2022). Various hypotheses exist that aim at explaining why negative traits expressed in psychiatric disorders have not been weeded out by natural selection. Space limitations prevent me from discussing the different hypotheses. However, most of the theoretical assumptions why negative traits persist in a population focus on the beneficial effects of particular traits involved, e.g., advantages of heterozygous individuals; trade-offs between adverse and fitness-enhancing traits; or linkage of negative with other, favorable traits. According to these assumptions, negative traits associated with schizophrenia are an unfortunate consequence of various mechanisms favoring beneficial traits, the latter being subject to positive selection. These hypotheses offer possible explanations why schizophrenia risk genes can still be found in a population´s gene pool. Importantly, most of these hypothetical explanations have a conceptual consensus at the core—they bestow causal primacy upon genes in *making* distinct traits. Thus, at the heart of the theoretical underpinning lies a deterministic role of the individual gene or sets of genes in *creating* phenotypic traits. This harks back to textbook examples of well-studied genes (e.g., those involved in monogenetic diseases) which shall not be the focus, here. Instead, in this paper, I will draw on insights from EvoDevo. Here, emphasis is given to developmental processes that are influenced by genes as "enablers of plasticity," not on genes as mere "trait generators." Rather than trying to elucidate a gene´s role "*for* " a given trait (or roles "*for* " multiple traits in case of pleiotropy), this alternative approach opts for a closer look at how genes serve developmental processes. As argued above, the definition of a gene "*for* " makes only limited sense in the wider context of developmental processes. Such explanatory shortcomings certainly also hold true for genes involved in neurodevelopmental diseases. When same gene product is part of several developmental modules and gets expressed at different phases during ontogeny, some genetic—or rather allelic—variants may not be eliminated by natural selection. Due to their crucial roles in developmental processes at another stage of development, these genes remain in the gene pool despite contributing to adverse effects (a type of trade-off). Examples how the same gene product can exert the same function, but still cause different effects during ontogeny come from sensitive (or critical11Space limitation prevents me from discussing the differences between critical and sensitive periods. For an excellent review see Knudsen (2004). Importantly, critical and sensitive periods operate by means of the same set of neural mechanisms (Hensch, 2004; 2005).) periods (see next section).

Let´s suppose that schizophrenia risk genes play crucial roles in neuroplasticity and in the regulation of sensitive periods of brain development. If this is the case, schizophrenia risk genes will be functionally active during various plasticity periods of development. The recurring activity might make these genes unassailable for negative selection if they have adverse effects only at one particular life stage but not at others. Similarly, these genes may escape negative selection when they contribute to pernicious trait development in periods of

high plasticity only when the organism is exposed to a certain environment but not when exposed to a variety of other environments. In other words, schizophrenia-susceptibility genes may confer plasticity and thereby variability to traits rather than being genes "*for* " positive or negative traits. In support of this view, it is now generally acknowledged that schizophrenia is a neurodevelopmental disorder of multifactorial causation. If risk genes for schizophrenia are the same ones that contribute to the regulation of plasticity involved in complex neuronal connectivity and brain maturation, this may account for the persistence of schizophrenia in the human population. Schizophrenia would then represent a costly trade-off in the evolution of temporal modules that comprise the same components (gene products, regulatory elements, etc.) which are recruited during development at different life stages22This is most likely not the only cause of the disease, but it may be an important one that has not yet received enough attention, in my opinion..

Let us return to the previously discussed *SRGAP2* gene. Intriguingly, genome-wide association studies and genetic linkage analyses have identified associations between variations in the*SRGAP2* gene (within the regulatory elements) and susceptibility to schizophrenia. It may, therefore, be tempting to say that the*SRGAP2* gene is a gene "*for* " schizophrenia. But in light of the discussion above, this seems as vague as saying that the*SRGAP2* gene is a gene "*for* " the expansion of the neocortex, or a gene "*for* " dendritic spine maturation, and so on. So, how can we better capture *SRGAP2* gene´s function and maybe also the function of other schizophrenia-susceptibility genes? As already mentioned, the *SRGAP2* gene is a multifunctional gene that contributes to cell proliferation, neuronal migration, axonal targeting, and spine maturation. The *SRGAP2* genes, specifically the*SRGAP2A* gene and its *SRGAP2C* paralog, are expressed during specific periods of brain development when the brain undergoes significant growth and reorganization. During these neuroplastic phases, the developing brain is also highly receptive to environmental inputs. Such phases of heightened plasticity are considered sensitive periods. Most noteworthy, it has been shown previously that activity of a newly discovered *SRGAP2* effector protein coincides with the opening of a critical period of plasticity in cortical pyramidal neurons (Assendorp*et al* ., 2024).

To sum up, I argue that researchers may have to rethink their understanding of the role of genes in the expression and development of diseases. Studying the genetic factors that contribute to psychiatric disorders, does not only require the formulation of a mechanistic explanation of specific gene functions, an elucidation of their spatiotemporal expression dimensions, and the identification how they contribute to gene regulatory networks or protein-protein interaction networks. It also necessitates a reappraisal of the very data under a philosophical and conceptual lens. This is where philosophy of biology might be helpful. Neuroscientists can take advantage of already established theoretical concepts that were honed through interdisciplinary discourse between EvoDevo scientists and philosophers.

Sensitive periods: phases of heightened plasticity

Developing brain circuits are particularly susceptible to external influences due to their high levels of neuroplasticity. The complex and more recently evolved circuitries of the human brain are risky targets of insults because of their complex gene–environment interactions and their intricate integration into brain circuits established earlier in development. Susceptibility to adverse impact is neither temporarily constant nor topographically linear across brain areas but strongly depends on specific windows of heightened plasticity that underlie the staggered brain maturation. Such sensitive periods vary across different brain regions and functions, yet share many important mechanisms and components.

Sensitive periods in neurodevelopment are crucial for shaping the brain´s structure and function. Disruptions during these periods due to genetic, environmental, or epigenetic factors can be devastating and increase the risk of developmental disorders. This is due to immature organisms adapting to environmental insults during sensitive periods by incorporating information permanently into their mature structure and function. This is in contrast to mature organisms that compensate insults by plastic responses in order to accommodate or buffer changes in the environment (Andersen, 2003). Consequently, focusing on neuroplastic, developmental processes that establish sensitive periods thereby contributing to the emergence of complex traits offer a different rationale than the classical genes-"*for* "-paradigm. Moreover, understanding the interplay between sensitive periods and the progression of neurodevelopmental disorders like schizophrenia can help identify

temporal windows for intervention and prevention strategies during which certain drugs (e.g., benzodiazepines or amphetamines) are particularly effective.

Sensitive periods can be subdivided into an initiation/opening phase, a plasticity phase, and a closing phase. Although, the boundaries between these phases are floating, the opening and the closing phase are clearly driven by differing phase-specific processes that ensure directionality. The onset of a sensitive period is usually triggered by a combination of environmental and genetic factors. Environmental factors refer to stimuli that are quite specific to the nature of the neural circuit in question, while genetic parameters include neurotrophic factors, hormones, transcription factors, and neurotransmitters. During the plastic phase, the ratio of excitatory to inhibitory synapses is crucial. The excitatory/inhibitory ratio decreases due to the maturation of GABAergic parvalbumin interneurons that innervate pyramidal cells. The rise in inhibitory activity significantly contributes to the sharpening and fine-tuning of cortical excitability as well as to the synchronizing of neuronal networks and evocation of gamma oscillations. Gamma oscillations facilitate complex cognitive functions, such as working memory and attention that continue to improve well into adulthood. While maturation proceeds, GABAergic signaling further increases thereby suppressing spontaneous, stimulus-irrelevant activity in favor of stimulus-driven inputs.

The plastic phase is strongly influenced by extrinsic cues that increase the signal-to-noise ratio and contribute to the reliability and efficiency of stimulus-evoked circuit activity (Hensch, 2005). Moreover, synaptic pruning contributes to the refinement and specialization of neural circuits for specific functions by reducing redundant synapses, strengthening relevant connections, and increasing accuracy by minimizing background noise. Pruning is mediated by genes of the complement system and other microglia-related genes that promote phagocytosis by microglia, genes of the major histocompatibility complex (MHC), proteolytic enzymes that degrade extracellular matrix components thereby facilitating the removal of synapses, and cytokines and chemokines that are expressed on microglia.

Eventually, the closure phase of the sensitive period is characterized by a stabilization of synapses. Synapses that have been reinforced by activation are stabilized by means of cell adhesion molecules that align pre- and postsynapses and consolidate synaptic connections. At the same time, molecular inhibitors are upregulated. When a circuit becomes efficient and reliable, stabilization occurs. This ensures consistent and optimized neural responses (and adaptive behavioral responses) to specific stimuli. The stabilization is achieved by preventing further plasticity by means of reduction of excessive pruning and rewiring. This last stage of the sensitive period is accomplished by the implementation of physical barriers to pruning and outgrowth, such as the formation of perineuronal nets on cell bodies and myelination of axons (Takesian & Hensch, 2013).

Sensitive periods: the case of schizophrenia

A significant number of genes that have been reported to be associated with schizophrenia (Butler *et al* ., 2016) also play a role during sensitive periods of development. For example, genes that mediate the shift of GABAergic neurons from being excitatory to inhibitory as well as a dozen genes that encode for $GABA_A$ receptor subunits and other neurotransmitter receptors as well as enzymes that catalyze neurotransmitters. In support of this, benzodiazepines that positively modulate $GABA_A$ receptor activity accelerate the onset of plasticity during sensitive phases by speeding up maturation of inhibitory transmission. Patients suffering from schizophrenia show a dysfunction of cortical GABAergic inhibitory circuits reflected by a higher excitatory/inhibitory balance as compared to healthy individuals (O'Donnell *et al.* , 2017). Furthermore, other genes that show association with schizophrenia concern the plasticity phase of development, especially those involved in synaptic pruning (Li *et al* ., 2022; Caseras *et al* ., 2024). In addition, genes that affect the closure phase of the sensitive period have been associated with schizophrenia (Willi & Schwab, 2013). Theses risk genes include genes that represent braking factors that affect the stabilization of synapses ensuring a persistent and balanced ratio of excitatory to inhibitory synapses (e.g., cell adhesion molecules) as well as the formation of perineuronal nets and myelination of axons. Interestingly, when axonal plasticity by myelin-derived restriction is impaired, brain plasticity persists and extends beyond the sensitive periods (McGee *et al* ., 2005; Yang *et al* ., 2012).

In neurotypical individuals, there is an increase in inhibitory transmission in the prefrontal cortex up to late adolescence. The decline in the excitation/inhibition ratio is paralleled by active readjustment of GABAergic transmission of interneurons innervating pyramidal neurons of the prefrontal cortex (Caballero *et al.* , 2021). This process fosters the integration of growing cortico-cortical signals based on complex social and environmental inputs occurring during this period. Being exposed to human-typical cognitive and social niches allows individuals to go through plasticity periods, so that brain areas involved in complex and abstract cognition can develop to acquire high-level thinking and social skills. For example, individuals require reliable social input to master complex skills, including the ability of abstract and symbolic thinking, decision making, and problem solving—all which include the prefrontal cortex. If the available information is heterogeneous or complex, an extended neuroplasticity process may be advantageous to acquire such higher-order cognitive thinking. The human cognitive niche usually enables this through social scaffolding (Caporael *et al* ., 2014). Due to increasing environmental and social demands that adolescents encounter, this developmental period is highly susceptible to adverse experiences that can alter the trajectory of the inhibitory system and render the prefrontal cortex hypofunctional. If individuals receive contradictory cues or a poverty of external cues, the duration of the sensitive window and thus plasticity may be prolonged as has been shown for the development of brain circuits involved in sensory processing (Fawcett & Frankenhuis, 2015). Similarly, an impaired excitation/inhibition balance can lead to impaired circuit stabilization and perpetually elevated plasticity (Carulli *et al* ., 2010). A developmental window that remains plastic confers higher vulnerability for individuals exposed to adverse conditions. Therefore, the closing of sensitive windows in a timely manner is crucial and usually regulated by braking factors. In fact, the functional maturation of the GABAergic system confers adult properties to the prefrontal circuit by means of excitatory/inhibitory balance. Interestingly, in patients suffering from schizophrenia, plasticity of the prefrontal cortex seems to extend beyond the sensitive period (McGee *et al* ., 2005; Yang *et al* ., 2012). This is supported by the findings of functional impairment of GABAergic parvalbumin interneurons in the prefrontal cortex of schizophrenics (Beasley & Reynolds, 1997).

A prolonged plasticity is particularly hazardous when at the same time synaptic pruning is still ongoing or even accelerated. Because both, accelerated and decelerated timelines result in diminished cortical organization (Szakács *et al* ., 2024) which ultimately can contribute to psychopathologies. In neurotypically developing individuals, the elimination of synapses occurs during the plastic phase of the sensitive period until braking factors set physical barriers by myelination and the formation of perineuronal nets that prevent further neuroplastic changes to the established networks. Normally, the process of synaptic trimming is crucial for the maturation of the prefrontal cortex thereby enabling many species-typical, high-level skills in humans due to reducing signal-to-noise ratio of synaptic inputs and increasing reliability and specificity of circuits. In people suffering from schizophrenia, however, adolescence coincides with an excess of pruning of synaptic connections in the prefrontal cortex which is probably causally related to a reduced frontotemporal and frontoparietal connectivity, a decreased dendritic branching, and an overall diminished number of synaptic connections (Keshavan *et al* ., 2020). In other words, schizophrenia may be the result of extreme "overpruning" at the prefrontal cortex. This phenomenon is either attributable to an acceleration of pruning processes during this late ontogenetic stage or to pruning processes that continue much longer due a disruption of braking factors at the late stage of sensitive periods. In support of the latter, a reduced perineuronal net formation was found in patients with schizophrenia (Berretta *et al.* , 2015; Enwright *et al* ., 2016; Mauney *et al.* , 2013). Thus, the pathological mechanisms of schizophrenia seem to involve an excess of synaptic pruning as well as an overall delay in closing of the sensitive period of development that causes a prolonged plasticity. These processes can be understood as trade-off effects of heterochrony. Under positive conditions, extended sensitive periods of heightened neuroplasticity of the neocortex allows the development of sophisticated, species-typical skills in humans adapted to their cognitive niche. In contrast, the heterochronic effects that have proven beneficial for the evolution of the species may induce detrimental neurodevelopment in individuals with schizophrenia-risk genes when they encounter adverse conditions in their sociocultural niche.

Being adapted to a niche ensures a temporal alignment between intrinsic maturational processes and envi-

ronmental input guiding brain development (Reh *et al* ., 2020). Sensitive periods in neurodevelopment are usually characterized by a changeover from intrinsic, experience-independent, and gene-governed mechanisms to experience-dependent mechanisms that are triggered and/or modulated by extrinsic inputs (Bourgeois, 1997). Complex behaviors depend on multiple sensitive periods. In fact, sensitive periods for low-level, more fundamental perceptual circuits end earlier than those for higher order aspects of perceptual circuits (Daw, 1997; Jones, 2000; Knudsen, 2004). This sequencing of sensitive periods is a fundamental neurodevelopmental principle as higher levels in brain hierarchy depend on precise and reliable information from lower levels in order to accomplish their functions. Subsequent sensitive periods require the timely progression of previous cascades of sensitive periods as well as non-random, circuit-specific experience. When individuals are deprived of adequate experience the opening of certain sensitive periods are delayed (Mower & Christen, 1985; Daw, 1997). The developmentally tightly regulated and stimulus-dependent progression of sensitive periods ensure high adaptability to a given environment by fostering adaptive wiring of the brain in response to highly specific environmental influences. This adaptability enabled by plastic responses allows the organism to integrate past information with ad-hoc sensory experiences and new, species-specific skills learned during ontogeny. The late sensitive periods in human development enable advanced cognitive abilities and further complex social behaviors. Some extraordinary human skills, including sophisticated language capabilities11Language development in humans is a complex, multi-stage process that typically spans from early infancy through late adolescence and early adulthood. The most sophisticated and refined aspects of language skills that develop in adolescence and beyond include abstract language use (e.g., metaphors, sarcasm, idioms) and specialized vocabulary related to specific interest and one´s social group., the ability of abstract and symbolic thinking, as well as the propensity for social collaboration and collective problem-solving are those that develop last during adolescence. And these skills are amongst the ones that are most strongly afflicted in schizophrenia. However, cascades of sensitive periods may cause cumulative effects of environmental insults. The impaired development of the prefrontal cortex may, therefore, also be the result of insults during earlier stages of ontogeny (e.g., pre- and perinatal stages) (Selemon & Zecevic, 2015). Or it may be the result of insults occurring at more than a single stage of development, as hypothesized in the "2-hit" model (Keshavan & Hogarty, 1999; Gildawie*et al* ., 2021).

Conclusion

Philosophers of biology have long challenged the classical genes-"*for* "-paradigm. The field of EvoDevo has traditionally benefitted from intense exchange between philosophers of biology, theoretical biologists, and empirical researchers. EvoDevo scientists now widely agree that the emergence of complex traits derive from developmental processes, often regulated by sensitive periods. Accordingly, "[neurotypic] brain function results from a conserved sequence of developmental processes of cell division, migration, network formation and maturation, directed by intrinsic genetic programs as well as by environmental and systemic cues, extrinsic to the nervous system. Within this sequence, appropriate stimuli induce events of heightened plasticity that are required to develop a given function" (Dehorter & Del Pino, 2020). These phases of heightened plasticity are particularly important in linking genetically guided developmental processes with intrinsic and extrinsic cues. By shaping traits in response to environmental inputs, sensitive periods can critically influence the trajectory of trait development. Alterations of neuroplastic processes can have advantageous effects as exemplified by heterochronic effects in hominid phylogeny that led to an evolutionarily driven expansion of the human neocortex. The dynamic aspects of traits are attributable to genetic and epigenetic regulation as well as environmental factors encountered in the species-specific niche. Complex interactions between genetic predispositions and environmental factors, such as upbringing, culture, or life experiences can have a tremendous impact on the manifestation of certain traits. Moreover, some behavioral traits might be more pronounced during stressful periods and manifest themselves in an extreme manner (Sullivan *et al* ., 2006). Yet, irrespective of extrinsic factors, traits can also exhibit significant variation due to varying expression that are intrinsically driven and occur at different developmental stages.

Developmental neuroscientists and developmental cognitive scientists have accumulated a wealth of data that corroborate the aforementioned framework. I believe that the time is right to get many more neuroscientists onboard. Rethinking the classical, deterministic paradigm of the gene–trait concept and working towards a

philosophical reconceptualization of traits as dynamic attributes tied to ongoing developmental processes, will provide a three-fold advantage:

- First, it allows a re-interpretation of a gene´s pleiotropic effects. Instead of focusing on the "intrinsic" functions of the respective gene, the dynamics and conditions of the spatiotemporal expression of the respective gene products (coding and non-coding sequences alike) become essential. This is an important conceptual shift from viewing genes driving processes to genes being *recruited* during ontogeny. Moreover, it is the specific developmental pathway that is of interest and less the individual component(s) of the pathway. In fact, some of the components of the pathway may be exchangeable. Because multiple genes contribute to a given process, gene products can compensate for each other at different steps. As a consequence, modular processes are better captured by systems biology rather than by mechanistic approaches that investigate linear effects. For example, positive feedback loops may be causally involved in the emergence of extreme traits when (small) perturbations in a system lead to amplification of the initial disturbance, resulting in increasingly exaggerated or self-reinforcing responses.
- Second, it will encourage a rethinking of manipulability and the effectiveness of interventions. Since most developmental processes enable compensatory effects (buffering effects or canalization) due to degeneracy, redundancy, or feedback mechanisms, many interventions will prove rather ineffectual. The challenges of compensatory effects are well known. By shifting the focus from fixed traits determined by genes to traits that unfold and change due to developmental processes, other means of interventions can be studied. These include changing the duration of a given process or shifting the start point or the end point of a given process.
- Third, by putting developmental processes in the center of the investigation, environmental variability will gain heightened importance. Rather than looking for the extrinsic trigger to express a certain gene, the whole developmental process needs to be taken into account. Environmental fluctuations can create selective pressures on developmental trajectories that vary over time. Environmental conditions can produce ontogenetic shifts that may be advantageous or neutral at some time point (e.g., the beginning of a developmental process). At a later timepoint, however, (e.g., at the cessation of the developmental process), environmental conditions may have changed and the outcome may be deleterious for the organism. There are many examples for stress-induced, altered developmental trajectories (e.g., often triggered by stressful environmental cues that are encountered prenatally or shortly after birth) that become maladaptive at a later developmental stage (Packard *et al* ., 2021; McEwen, 2013). This alternative view also concerns therapies for neurodevelopmental disorders that might focus more closely on how genetic and environmental variations influence the rates and timing of developmental trajectories and milestones in children and adolescents, and causes of variability among individuals.

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