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RECENTERING NEUROSCIENCE ON BEHAVIOR: THE INTERFACE BETWEEN BRAIN AND ENVIRONMENT IS A PRIVILEGED LEVEL OF CONTROL OF NEURAL ACTIVITY

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Abstract

Despite the huge and constant progress in the molecular and cellular neuroscience fields, our capability to understand brain alterations and treat mental illness is still limited. Therefore, a paradigm shift able to overcome such limitation is warranted. Behavior and the associated mental states are the interface between the central nervous system and the living environment. Since, in any system, the interface is a key regulator of system organization, behavior is proposed here as a unique and privileged level of control and orchestration of brain structure and activity. This view has relevant scientific and clinical implications. First, the study of behavior represents a singular starting point for the investigation of neural activity in an integrated and comprehensive fashion. Second, behavioral changes, accomplished through psychotherapy or environmental interventions, are expected to have the highest impact to specifically reorganize the complexity of the human mind and thus achieve a solid and long-lasting improvement in mental health.

Keywords: behavioral sciences, ethology, complexity, emergent properties, process, network, evolution, mind, philosophy, causality, reductionism

1 State-of-the-art

1.1 The limits of the reductionist approach in the neuroscience and mental health fields

In the last decades, neuroscience made monumental advancements in the understanding of the cellular and molecular processes that regulate brain activity. These advancements have been driven by huge technical innovations that allowed to investigate details of the central nervous system that were unthinkable only few years earlier (Altimus et al., 2020; Kanter et al., 2022). Accordingly, the common view of the future progress in brain sciences relies on novel technical advances that will afford to study the molecular and cellular machinery with unprecedented resolution, reconciling modifications at different levels, from genes to brain circuits and behavioral outcome. Nonetheless, our capability to understand and treat brain alterations linked to mental illness through a molecular approach is still arduous and imprecise and translating the increasing scientific knowledge into novel and effective therapeutic strategies for brain disorders has advanced only limitedly (Hyman, 2012; Murray et al., 2021; Scannell et al., 2012). In addition, pharmacological research in the last decades did not meet the expectations raised by the success achieved in the middle of last century (Institute, 2019).

Among the reasons of the limited progress in treating mental illness has been the pursuit of developing treatments mainly by exploiting a reductionist approach and thinking of the brain as a mechanistic system in which independent components with distinct functions can be controlled and manipulated (Maggiora, 2011; Van Regenmortel, 2004). This view, named the *upward causation model*, posits that processes at lower scales explain and define processes at higher scales (Noble et al., 2019). Accordingly, when a specific component goes awry, the administration of a drug can reinstate its function, thus promoting mental health. Causality models of this kind are satisfying since they align with our mechanistic worldview and mirror the design of man-made systems, such as machines or electronic circuits. However, there is a growing awareness that highly complex systems as the human mind cannot be easily decomposed into discrete modules executing sequential and causally linked operations (Wolff and Olveczky, 2018). In the words of Gregory Bateson, "the major problems in the world were the result of the difference between how nature works and the way people think" (Bateson, 1972). Indeed, the brain structure comprises systems characterized by recurrence, feedback, interconnectivity and interdependency to a degree that makes localization of function and the notion of causality less intuitive and explanatory. Therefore, even if the reductionist approach has been impressively productive and continues to deliver outstanding results in the understanding of brain function and structure, the complexity of the mind requires an uneasy paradigm shift (Gardner and Kleinman, 2019; Kendler, 2012; Miller, 2010; Van Regenmortel, 2004).

2 Facing complexity

2.1 No privileged level of causation

According to reductionism, the direction of causation is mainly univocal and well defined: genes and molecules occupy a privileged position and an upward causation process occurs -- from molecular to the organismic scale (i.e. from the lower scale to the higher scale; Dawkins, 1976). The theoretical consequence of this view is that the regulation of the processes at the molecular scale allows for overall control of the physiological and pathological states. However, increasing evidence challenges such a view when applied to complex phenomena as psychiatric disorders.

A seminal paper by Sapolsky and Salt (Sapolsky and Balt, 1996) elegantly showed that the information needed to originate a complex biological process cannot be located exclusively at molecular scale, but it is distributed across scales. They analyzed the literature relevant to the role played by testosterone in aggressive behavior from the molecular to the organismal scale and demonstrated that investigating the scientific issue at the molecular scale does not provide a more exact description than at any other scale, indicating that biological phenomena are not originating at a specific scale but take place across scales and emerge from their interaction.

More recently, Denis Noble has proposed the Principle of Biological Relativity (Noble, 2012). In line with what previously suggested by Richard Lewontin (Lewontin, 2000), it posits that there is no privileged level of causality across the multiple scales of networks that define the organism: any part of a network at any level might affect every other part (Noble, 2012). In other words, the principle proposed by Denis Noble involves multiple levels of causation, adding the *downward* to the upward causation model: any level of the organization of the organism can be the starting point for a causation process. In order to stress the coexistence of different causation models that ties together the constituents with the whole, it is worth to quote a metaphor from *Invisible cities* by Italo Calvino (Calvino, 1978):

Marco Polo describes a bridge, stone by stone.

'But which is the stone that supports the bridge?' Kublai Khan asks.

'The bridge is not supported by one stone or another,' Marco answers, 'but by the line of the arch that they form'.

Kublai Khan remains silent, reflecting. Then he adds: 'Why do you speak to me of the stones? It is only the arch that matters to me'.

Polo answers: 'Without stones there is no arch'.

2.2 Downward causation

Complementary and opposite to the upward causation, the downward causation model posits that the constraints of function imposed at high scales organize and define the processes occurring at lower scales. A telling example comes from the work by the German embryologist Gerhard Fankhauser on the triton *Notophthalmus viridescens* larvae (Fankhauser, 1945; Uversky and Giuliani, 2021). Tritons go through spontaneous polyploidization (i.e. modification of the number of sets of chromosomes). As a consequence, perfectly healthy individuals differing for their polyploidy differ in the size of the cells they are made up (e.g. polyploid individuals have cells that are almost double sized compared to those of diploid individuals). Fankhauser investigated the consequences of such cell size difference on the triton larva protonephrons and found out that all individuals, independently from the cell size, have overlapping organ size and structure. This is achieved by making up the protonephron structures with different numbers of differently sized cells: protonephron from polypoid individuals are made up by around half the number of cells of those from diploid individuals. Such preservation of protonephron structure is because *function is key for life* and function is assured by the size and thickness of the protonephron ducts and not by the number of cells building them. The size and thickness of the ducts are indeed finely tuned by the features of body fluids, a downward constraint that cannot be defined by upward causation (e.g. cell size; Fig. 1a). As a simple logical analogy, the size of the rooms in a house is not defined by the size of the bricks but by the function of the room. For instance, a standard house room is around 3.5 meters high because such height fits with its function (e.g. comfortably hosting people) and the bricks are used accordingly (Fig. 1b). Fankhauser's findings were unexpected to Albert Einstein, a colleague of him in Princeton, who wrote: *Most peculiar, however, for me is the fact that in spite of the enlarged single cell the size of the animal is not correspondingly increased. It looks as if the importance of the cell as ruling element of the whole had been overestimated previously.* (Fankhauser, 1972). Fankhauser's seminal work has been largely overlooked but it is an elegant and effective example of downward causation urging the investigation of the molecular or cellular processes considering how the whole phenomenon is organized and how it behaves when embedded in its environmental context (Kim, 1999). It is the function of a biological process, and therefore the context in which the process takes place, that constrains and organizes the constituents (Fig. 1; (Noble et al., 2019).

Though in the last half century the acclamation of the reductionist causal chain obscured the relevance of downward causation, it constantly emerges as a key concept to understand living organisms. For instance, the complete deletion of up to 80% of genes in the yeast has no obvious phenotypic consequence in a rich medium. However, when the environmental context is considered, the function of the deleted genes for individual survival emerges (Hillenmeyer et al., 2008). It is the environmental context that determines the consequences of gene modifications. Similarly, in mice housed in standard laboratory living conditions, the deletion of specific genes has been reported to be even advantageous. However, when facing the challenges of the natural environment, the lack of the function due to the same gene deletions led to a significantly reduced survival rate (Giorgio et al., 2012). As an example in the neuroscientific field, birds have small brains densely packed with tiny neurons whose number (Olkowicz et al., 2016), and connectivity layout (Stacho et al., 2020) is overlapping to that of mammals. Presumably, aerial environment acts as a constrain that requires lightweight brain to allow birds to fly.

With regard to complex behavioral responses and their underlying mechanisms, these also can be investigated and understood only when the downward causation perspective is considered (Lipp and Wolfer, 2013). In preclinical models, the eco-ethological context is indeed key for an appropriate interpretation of the effects of genetic manipulations affecting behavior. The deletion of the gene coding for the RNA BC1, a small non-messenger RNA common in dendritic microdomains of neurons, produces behavioral changes interpreted as apparently beneficial in laboratory settings, such as a modification of fear to novelty (Lewejohann et al., 2004). However, in naturalistic conditions, the functional consequences of the gene deletion revealed to be dysfunctional (Lipp and Wolfer, 2013). Similarly, the deletion of the trkB neurotrophin receptor in mice produced alterations in behavioral flexibility that were not possible to identify if not tested in naturalistic settings (Vyssotski et al., 2002).

2.3 Emergent properties: specificity and causality revisited

Downward causation is highly relevant because organisms are complex systems defined by emergent properties that cannot be explained, or even predicted, by studying the individual constituents of the organism (Van Regenmortel, 2004). In other words, none of the constituents summarize the behavior of the emergent property and the relation between the whole and a constituent is not stable and not proportional. This has highly relevant theoretical implications and redefines key concepts used in the neuroscience and mental health fields:

1) *Specificity*: no emergent property is specifically related to any of its components. A complex biological activity such as a behavioral response does not arise from a specific constituent (e.g. a gene, molecule, pathway, neuron, circuit, etc.). The same constituent is involved in multiple other processes. For instance, genes involved in cognition, as those regulating synaptic activity, are not specific for cognition but play a role in many other brain functions and behavioral domains. Therefore, it is not possible to control the emergent property by controlling a specific gene, molecule or any other constituent. Instead, specificity arises from the interplay among the constituents participating to the emergent property.

2) *Causality*: emergent properties have causal powers that are not reducible to those of their constituents. Therefore, constituents cannot establish direct causal relations with those phenomena causally related to the emergent property. So, when emergent properties take place, it is not possible to study their causal relations by analyzing any single constituent alone. Constituents at different levels (e.g. genes, cells, circuits, etc.), which altogether produce an emergent property as a behavioral response (e.g.

fear), have no direct and linear relationship with the emergent property itself and consequently with the events causally related to the emergent property (e.g. fight or flight).

In light of this view of specificity and causality, when investigating emergent properties as physiological and pathological behavioral responses, simple approaches based on the upward causation model, as a genotype-phenotype map should be replaced by theoretical frameworks based on complexity which consider concepts as relationship, context, instability and non-linearity. Accordingly, the traditional reductionist view of individual agents at microscopic level (e.g. genes, molecules, circuits, etc.) as difference-making causes of macroscopic-level phenotypes has to be reconsidered (DiFrisco and Jaeger, 2020). As an extreme example of the lack of match between microscopic changes and macroscopic consequences, people lacking most of their cortex after a developmental hydrocephalus can preserve most of their intellectual capacities (Feuillet et al., 2007).

It is however worth mentioning that not all phenomena are emergent properties. Many can originate from simple events, as monogenic disorders. In this case, reductionism reveals as the most appropriate theoretical approach (Fig. 2).

3 The need for novel approaches

Because of the limits of reductionism in investigating the complexity of living organisms, an alternative approach is warranted. However, which approach should be used is still questioned. A general holistic approach based on the view that everything is connected does not provide a clear theoretical and methodological alternative. Thus, we need novel conceptual tools able to specifically address complexity by identifying structures and features of systems that can be experimentally explored and measured. These go beyond and in parallel with the development of increasingly powerful techniques, including high-throughput and highly sensitive omics methods and bioinformatics, which are currently providing tons of data but are not renewing the theoretical framework needed to face complex biological problems.

The conceptual tools to study complexity are being developed rapidly in biomedicine. They are both methodological and theoretical and consider key notions such as emergence, relations, nonlinearity and self organization. A telling example is the seminal and elegant work on networks in biology (Barabasi, 2012;

Barabasi and Oltvai, 2004) and in mental health (Borsboom, 2017) which investigates the patterns of relations as key features of phenomena. For instance, these approaches conceptualize disorders as systems of causally connected symptoms, which are mutually interacting elements of complex networks that do not share a single causal background (Borsboom and Cramer, 2013). However, novel approaches are still explored and their appropriateness and effectiveness are highly debated (Borsboom et al., 2018; Krakauer et al., 2017).

4 The interface: a privileged level of control

Given that emergent phenomena, as behavioral responses and psychiatric disorders, originate from non-linear interactions at multiple scales and have no or limited direct causal relations with their constituents, a major issue in the neuroscience and mental health fields is where to start to explore the output of complex systems as the human brain. As mentioned above, there is no privileged level of causation (Kendler, 2012; Noble, 2012). However, a privileged level of control and orchestration of the system can be identified. This represents a starting point for the system investigation and understanding.

4.1 Identifying elements allowing for control of the system

Biological systems can be seen as a complex set of nodes connected to each other. While most of the nodes limitedly affect the others, some regulate a large proportion of them in a coherent fashion. Consequently, the control of the latter allows for the control of the entire system and its activity. As the human brain is a system it can be hypothesized that by controlling selected key nodes it is possible to coherently regulate neural activity (Fig. 3). A metaphor used by the network theory expert Albert-László Barabási can help illustrate this point (Liu et al., 2011). A car is made of around 5,000 components. To control this relatively complex system, not all components have the same relevance, but the regulation of three to five car parts—the steering wheel, the gas pedal, the brake, and in Europe also the clutch and shifter – gives the driver full control of the car allowing to drive it anywhere a car can go. It is worth noting that these key parts share a highly relevant feature: they are at the interface between the system (i.e. the car) and what is outside the system (i.e. the driver; Fig. 3a). Such view can be generalized to any system and the nodes at the interface between the system and its environment are crucial for system control. Back to neuroscience, the interface between the central nervous system and the individual's environment is the behavior. Therefore, behavior is a major controller and an orchestrator of the neural processes, representing a unique level of investigation to understand brain activity and organization (Fig. 3b). This concept can be generalized to other biological systems (Fig. 3c; see paragraph 8.3 for details).

4.2 The prominent role of evolution and context

The importance of the interface has been previously stressed out (Arora et al., 2020). However, when and why the interface becomes relevant for controlling the system warrant further consideration. The interface is shaped and becomes effective through the evolutionary process, which defines its role in matching environmental challenges to specific responses by the system (i.e. the organism; Fig. 4). By contrast, components not shaped to be the interface by evolution have no or limited control power. Going back to the analogy of the car used by Barabàsi, the key role played by the interface (i.e. the steering wheel, the gas pedal, the brake) in controlling the car is relevant because the system (i.e. car) has evolved (by engineers) to interact in a coherent fashion with the outside of the system (i.e. the driver). It is worth nothing that the car behavior can be affected also by parts not at the interface, such as the carburetor. However, in this case the control is not subtle allowing only to prevent the car to move but not to drive it to a specific goal. Likewise, complex systems as the brain are affected by modifications in nodes at many scales (e.g. genes, molecules, areas). For instance, electric stimulations of selected brain areas is able to trigger neural activities corresponding to specific motor and emotional responses (Caruana et al., 2018). However, a fine control of the central nervous system is achieved only by affecting the nodes at the interface, such as the behavioral responses.

A second key factor determining the relevance of the interface in controlling complex systems is the context. The interface exerts a subtle control only when the context in which it operates is the one for which the interface has evolved. Back again to the metaphor of the car, if it is out of its evolutionary context as driving on ice instead of on road, no or limited control can be exerted via the interface.

5 Behavior controls the brain

As mentioned above, when applying the concept of the interface to the field of neuroscience and mental health, behavior emerges as key since it is the interface between brain activity and the environment. Here, the term behavior means all the actions and associated mental states made or experienced by the individual in the interaction with the environment. Therefore, *behavior is a privileged level of control of brain activity* (Fig. 3b). This becomes obvious when considering that the implementation of the appropriate behavioral responses (e.g. reproduction, nutrition, defense, etc.) is the ultimate arbiter of the individual's survival and fitness. These behavioral responses, in turn, select for the combination of brain elements at molecular, cellular and systemic levels that best serve them. Indeed, according to the downward causation, the same behavior and the accompanying mental states can be achieved across individuals recruiting different subgroups of neural elements selected according to the biological features, personal history and living context of each individual (Cassiers et al., 2018). Therefore, behavior controls and orchestrates brain activity and not vice versa. No single or subgroup of brain elements coherently and subtly controls behavior, yet the latter is produced and constrained by the elements of the central nervous system.

5.1 Psychotherapy and mindfulness

Since the XIX century, it is known that psychotherapy has a profound influence on emotional state and behavior (Holmes et al., 2018; Marks, 2017). Recently, an increasing number of studies is showing that it also produces significant functional and structural modification in the brain (Barsaglini et al., 2014; Mason et al., 2016). Over the past decades, the progress in neuroimaging techniques has allowed to investigate brain modifications induced by psychotherapy. These studies showed that the progress and outcome of psychotherapy produce neurobiological modifications as a normalization of altered neural activity patterns and/or a recruitment of areas not already activated. For instance, the fronto-limbic circuitry has been found involved in both depression and its psychotherapeutic treatment (Brody et al., 2001; Dichter et al., 2010; Fu et al., 2008; Goldapple et al., 2004; Kennedy et al., 2007). Alternatively, psychotherapy produces compensatory changes in areas not previously impaired as in post-traumatic stress disorder patients (Beutel et al., 2010; Prasko et al., 2004; Sakai et al., 2006). In addition, often the effects of psychotherapy overlap those of medication (Mechelli, 2010). However, such overlap is reported only by part of the studies (Apostolova et al., 2010; Nakao et al., 2005). Finally, changes in brain activity have been reported to be an effective mean to monitor the progress and outcome of psychotherapy (Schienle et al., 2009) and to predict treatment outcome (Brown et al., 2021; Mason et al., 2017).

A further approach able to modify how the individual interacts with the environment is mindfulness meditation (Greenberg et al., 2017; Mooneyham et al., 2016). Though the findings are still debated owing to the diversity of operational definitions of mindfulness and the discrepancies in the analysis of neural changes, an increasing number of studies indicate that mindfulness is associated to important structural and functional brain modifications (Baltruschat et al., 2021). These include an enhancement of functional connectivity among brain regions within the default network (Mooneyham et al., 2016; Zhang et al., 2021), an increase in grey matter that directly correlates with the amount of meditation training (Holzel et al., 2008), and a reduction in amygdala activity in response to threats (Dutcher et al., 2021). In addition, mindfulness changes the circulating levels of inflammatory markers (Dutcher et al., 2021), showing that it affects the entire body physiology which, in turn, may participate in regulating brain activity (Branchi et al., 2021).

5.2 Lifestyle and physical activity

Lifestyle, including diet, sleep and smoking habits, has been reported to affect brain structure such as gray matter volume (Opel et al., 2020; Scullin, 2017). A magnetic resonance imaging study aimed at assessing the age of the brain analyzing the UK biobank datatset showed that gray-matter volume and white-matter microstructure measures are affected by lifestyle (Cole, 2020). A decreased gyrification in left premotor and right prefrontal cortex, and higher functional connectivity to sensorimotor and prefrontal cortex were found associated to the combination of differentially contributing lifestyle variables. It is of interest that these effects have been found to be independent of genetic contribution (Bittner et al., 2019).

Physical activity has also an important impact on the central nervous system (Erickson et al., 2014). Studies consistently show that exercise is associated with enhanced functional and structural connectivity within the brain and increased gray matter volumes in the prefrontal cortex and the hippocampus. These results suggest that the positive effects of physical activity on cognitive outcomes might be associated to brain changes (Rolandi et al., 2016; Won et al., 2021).

5.3 Experience and learning

Experience and acquiring new skills mold the function and structure of the central nervous system during the entire lifespan, indicating that neural changes induced by behavioral changes, though overall more pronounced during selected developmental windows, occur also during adulthood. Changes in white matter have been shown even after very brief behavioral interventions lasting hours (Ekerdt et al., 2020; Hofstetter et al., 2017; Huber et al., 2021; Sampaio-Baptista and Johansen-Berg, 2017). The acquisition of a new skill, such as learning a new language or training to navigate in a complex environment, results in structural grey and white matter changes that can be observed within months or even weeks from the experience (Draganski et al., 2004; Elbert et al., 1995; Maguire et al., 2000). Brain connectivity shows important modifications as well, both at synaptic and system levels (Olsen and Robin, 2020). Learning involves the reinforcement of neuronal connections (Dudai, 2004) and changes in the relationship between functional brain areas (Passiatore et al., 2021).

5.4 Criticisms to behavior controlling brain activity

Criticisms have been raised to the view of behavior controlling brain activity. First, many studies did not describe a direct causal link. However, increasing evidence is demonstrating that brain modifications are causally related, predictable and directly proportional to the behavioral changes that induced them (Castegnetti et al., 2021; Geng et al., 2021; Mason et al., 2017; Tost et al., 2015; Tost et al., 2019). Other criticisms concern the limited overlap of brain modifications induced by similar experiences across individuals and studies (Apostolova et al., 2010; Nakao et al., 2005). This discrepancy has been interpreted as an indication that therapeutic strategies aimed at achieving a behavioral change are not a reliable method to modify brain activity and thus to treat psychiatric disorders. However, such interpretation is based on reductionistic causal chain by which psychopathology is caused by a specific component that goes awry and the reinstatement of its function promotes mental health. As previously discussed, this view is increasingly challenged by recent findings and, in line with the personalized approach, any individual may show a different combination of brain modifications, constrained by its personal history and biological background, to achieve recovery (Cassiers et al., 2018). Furthermore, an exact match between specific brain constituents or circuits and behaviors is increasingly questioned (see Fig. 2 and next chapter). Finally, the view of behavior as privileged level of control of brain activity is in line with its power in predicting complex physiological processes as the response to stress (Rodrigues et al., 2020).

6 No single of subgroup of neural elements controls behavior

Despite many studies have been aimed at identifying neural elements controlling complex behavioral responses, increasing evidence shows that such reductionist relation is unlikely (Krakauer et al., 2017). Behavior is an emergent property and thus cannot be investigated by dissecting its lower-level components because these have no or limited causal relationship with it. Indeed, it has been shown that, on the one hand, different activation patterns/involvement of brain elements are able to produce the same overall response (Prinz et al., 2004). On the other, the same behavior does not univocally involve the same structure or pattern of neural activity. The same group of neural elements can switch among different ways of interacting, thus producing radically different outcomes (Sakurai and Katz, 2017; Takemura et al., 2017). One of the most striking examples to illustrate the fundamental epistemological difficulty of deriving emergent properties as behavior from the neural elements concerns the roundworm (*Caenorhabditis elegans*). Even the full description of the genome, cell types and interactions in relatively simple brains is not enough to explain and predict behavior. The diagram of the interactions between the 302 neurons of the nervous system of *Caenorhabditis elegans* has been fully detailed (Bargmann, 1998). Yet, it is not sufficient to describe how neurons interact to produce the behavioral outcome, demonstrating that it is extremely arduous to infer behavior from the neural properties (Badre et al., 2015; Cooper and Peebles, 2015; Gomez-Marin et al., 2014; Krakauer et al., 2017). Therefore, the investigation of brain activity and organization is effective when starting at the behavioral level and assessing which neural structures and processes are recruited by selected behavioral responses while, with few exceptions, the opposite approach is often inconclusive. This is in line with studies showing that approaches based on the analysis of single or subgroups of neural elements has limited power for the meaningful understanding of the overall outcome of the central nervous system, regardless of the amount of data (Jonas and Kording, 2017).

7 Environment shapes behavior

7.1 The prominent role of the environment in defining behavior: the gene x environment interaction revisited

The environment is a key player in defining behavior, and thus mental health (Branchi, 2011; Branchi and Giuliani, 2021; Tost et al., 2015). Its action occurs in interaction with genes or, more in general, with the biological features of the organism (Caspi and Moffitt, 2006). However, the marked conceptual difference in the contribution of the environment and of the biological counterpart in the frame of this interaction is often overlooked. Along the evolutionary process, the environment shapes coherent and well-orchestrated behavioral responses able to face its challenges (Fig. 4). By contrast, no single or group of genes has been selected to be the sole orchestrator of complex behaviors. Consequently, the environment is a major driver of the behavioral outcome while the genes have limited power in defining it. The genes mainly code for the neural elements that allow the behavior to occur. In other words, behavioral responses and environmental conditions match each other but behavioral responses are not specifically related to selected genetic or molecular elements. Consequently, environmental interventions are powerful tools to produce well-defined and specific modifications of the behavioral outcome, and thus effectively treat psychopathologies. By contrast, molecular or genetic modifications produce very broad and potentially unpredictable effects at behavioral level (Fig. 5). Nevertheless, both approaches are highly relevant to help psychiatric patients.

The role of the environment in orchestrating behavior, and therefore mental health, has been widely reported (Rutter, 2005; Tost et al., 2015; Viglione et al., 2019). Adverse conditions have been shown to increase the vulnerability to psychiatric disorders, while favorable experiences promote resilience. For instance, a proxy of the quality of living conditions as socioeconomic status accompanies differences in mental health (Farah, 2017). As further example, living in urban areas and being exposed to the associated conditions leads to an increase in psychiatric disorders (Peen et al., 2010). Conversely, natural environments have beneficial effects on a variety of mental health outcomes (Bowler et al., 2010; Tost et al., 2015).

7.2 The relevance of the environment is amplified by neural plasticity

Plasticity is the capacity of the nervous system to modify its activity and structure in response to experience (Branchi, 2011). Such a definition implies the ability of the brain to change itself but not to define the form that such change should take. A higher or lower degree of plasticity simply renders the brain and behavior, respectively, more or less susceptible to change according to the quality of the environment (Branchi and Giuliani, 2021). As a consequence, enhanced plasticity has not a beneficial effect *per se*, but its value must be estimated according to the environmental context (Branchi, 2011). Accordingly, the outcome of treatments or interventions enhancing plasticity depends on the quality of the environment and consists in the amplification of its impact on behavioral outcome (Alboni et al., 2017; Carhart-Harris et al., 2018; Viglione et al., 2019). For instance, selective serotonin receptor inhibitors, the most used antidepressant drugs, enhance neural plasticity and thus amplify the impact of the living conditions on mood in a dose dependent fashion (Chiarotti et al., 2017; Klobl et al., 2022; Reed et al., 2022; Viglione et al., 2019). Based on this view, the relevance of the environment in shaping behavior and thus mental health is even greater when exploiting interventions or treatments able to enhance neural and behavioral plasticity (Branchi, 2011; Branchi and Giuliani, 2021).

8 Implications for the treatment of psychiatric disorders

An approach to neuroscience and mental health centered on the view of behavior as privileged level of control of neural processes holds the promise to advance the understanding of the mechanisms underlying psychiatric disorders and to foster the development of novel therapeutic strategies.

8.1 Resilience emerges from behavioral change

Stress-related disorders are a huge medical and social burden (Wittchen et al., 2011) with direct and indirect economic costs estimated around €300 billion per year in Europe alone (Olesen et al., 2012). Among the most promising strategies to cope with such burden is promoting resilience defined as achieving a favorable outcome in the face of adversity (Branchi and Giuliani, 2021; Ungar and Theron, 2020). Resilience consists of a dynamic process involving the acquisition of cognitive abilities and/or emotion regulation that ultimately results in effective coping mechanisms. It is important to emphasize that, though also biological processes are fundamental, resilience is mainly promoted via behavioral changes that, in turn, produce important brain modifications (Grueschow et al., 2021; Kalisch et al., 2017; Kalisch et al., 2015). The increasing impact of resilience to prevent and treat psychopathology is in line with the relevance of the view of behavior as controller of neural activity. This relevance is corroborated by studies from different brain research fields such as those demonstrating the critical action of behavioral interventions on brain activity and structure in patients with neurodegenerative disorders (Chandler et al., 2019) and psychiatric disorders (Mason et al., 2017).

8.2 The environment gap

Given the role of the environment in shaping behavior and the associated mental states, it is a key factor in the comprehension and treatment of psychiatric disorders (Tost et al., 2015); see paragraph 7). Accordingly, therapeutic strategies based on environmental interventions as green care or social farming are increasingly exploited (Borgi et al., 2019; Vera, 2020). However, the environment is still often overlooked in psychiatry and neuroscience research fields. This dramatically reduces the reliability, explanatory potential and impact of studies aimed at understanding psychopathology and at developing novel therapeutic strategies. For instance, with some important exception (Trivedi et al., 2006), clinical trials in psychiatry do not consider the details about the environmental conditions in which patients live. Given that genes and neuronal processes do not act by themselves but need to be regulated by signals from the environment, investigating the relevance of neural mechanisms overlooking the patient's living conditions reduces the opportunity to capture clinically relevant features able to make biological processes become of clinical significance and of benefit to patients (Schumann et al., 2014).

8.3 *Interfaces: analogies from other research fields*

The interface is a privileged level of control of any system because all systems have evolved to respond to the information decoded via the interface. Therefore, behavior is not an exception, but all the interfaces between our environment and us shaped by evolutionary processes represent a potential privileged level of control of our brain and body processes. The immune system is a telling example (Fig. 3c). Though we are fighting cancer since centuries, the efficacy of therapeutic strategies has tremendously increased when we started to exploit immunotherapy (Zhang and Zhang, 2020). Instead of directly targeting the huge complexity of this class of diseases, immunotherapy consists in harnessing the immune system, which is the interface between the organism and infective agents or other diseases, to eradicate cancer and prevent its recurrence. In this context, the identification and the understanding of the molecular machinery underlying cancer are less relevant. Immuno-oncology has represented one of the most relevant successes in biomedicine ever (Demaria et al., 2019). Other interfaces, such as nutrition and microbiota, represent other very promising research areas for the development of novel therapies as well (Sherwin et al., 2018).

9 The interface approach

Broadening the perspective, an *Interface approach* is compelling to the study of the complex systems as the human brain. Interfaces at any scale and in any system are places where the system structures and activities are highly organized to allow an effective interplay between the system and its external world. This organized complexity, resulting in greater simplicity (Crutchfield and Wiesner, 2010), makes the study of interfaces a unique starting point to explore and understand complex systems and their emergent properties (Fig 6). A telling example is brain organization that is relatively simple and easy to unravel when immediately involved in activities at the interface with the environment, such as vision (Hubel and Wiesel, 1962) and the somatosensory system (Woolsey and Van der Loos, 1970). In addition, since interfaces are the ultimate outputs of the system, because of downward causation they are a privileged level of control of the system activity. As an analogy, machine learning, similarly to behavior, is a process able to evolve according to the effectiveness of its outcome. The strategies developed by machine learning during the learning process are unknown and cannot be directly targeted to modify its outcome. By contrast, the way the learning process is organized can be easily affected by intervening at the machine-human interface, that is training machine learning to produce a different performance. This is in line with the idea of intervening on behavior, through psychotherapies or environmental interventions, to control and modify brain activity.

10 Conclusions

Mental wellbeing and psychiatric disorders are complex phenomena and the reductionist approach falls short in tackling them (Borsboom et al., 2018; Gomez-Marin et al., 2014; Jonas and Kording, 2017; Krakauer et al., 2017). Thus, alternative and complementary theoretical views to address complexity in brain sciences are warranted (Borsboom et al., 2018). Here, I propose to recenter the neuroscientific and psychiatric research on behavior because -- since behavior is the interface between the central nervous system and the environment -- it is a privileged level of control of brain activity and therefore an orchestrator of neural processes. This view has relevant scientific and clinical implications. First, behavior and the associated mental states are a unique solid starting point to investigate and understand the human brain because only the behavioral level allows to explore brain function as a whole, providing a comprehensive picture of the contributions of the involved genetic, molecular and neural elements. Investigations of neural elements at any other level are highly informative to explore specific neural features but have limited impact for understanding behavioral outcome and mental health. Second, changes in behavior, achieved through psychotherapy or other interventions, have the highest impact to finely reorganize the complexity of the human mind and thus achieve a solid and long-lasting modification in neural activity, switching from psychopathology to mental health. This does not imply that pharmacological drugs and other treatments targeting specific neural element or circuits should be disregarded as relevant tools to treat disorders and improve wellbeing. These are of paramount importance for the clinics *per se* and in combination with other therapeutic approaches. Third, behavior is the meaningful level for assessing brain output in mental health research. A healthy brain producing a diseased behavior or vice versa is meaningless. Finally, in the light of the preceding, disciplines aimed at measuring and understanding behavior, as behavioral sciences and ethology, are essential for the progress of basic and applied neuroscience in order to understand the brain, unravel the bases of brain disorders and develop effective therapeutic strategies.

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Figure legends

Figure 1. Downward causation. (**a**) Tritons (*Notophthalmus viridescens*) go through spontaneous polyploidization and perfectly healthy individuals differ, according to their polyploidy, in the size of cells they are made up. In particular, polyploid cells are larger than diploid cells. This condition may theoretically lead to two different organ structures in polyploid individuals: (1) if the number of the cells is equal, the size of the organ, as the protonephron ducts, will be larger than that of the diploid individuals. Alternatively, (2) if the number of cells is reduced, the size of the organ will be comparable. However, since *function is key for life* and is assured by the size of the organ, only the second organization, which preserves the organ size and thus function, is compatible with life and will be selected by the evolutionary process. Therefore, function constraints and instructs the organization of microscopic structure of the individual. (**b**) As a simple logical analogy, the size of a house should not be defined by the size of the bricks but by its function. A house with doors of four meters of height and ceiling of 6 meter of height would not preserve its function. See text for further information.

Figure 2. Causal links between constituents and functional outcomes. The features of constituents (i.e. healthy or diseased) do not univocally lead to the integrity or loss of function. **(a)** Healthy condition. **(b)** Diseased constituents have a direct causal relationship with the disorder. In this case, reductionism is effective at identifying the cause of function loss, e.g. a specific microscopic component (e.g. genetic, molecular) that goes awry, as in monogenic disorders. In complex disorders, as psychopathologies, **(c,d)** the interplay among processes at the multiple levels of organization within the brain and **(e,f)** the interaction between the individual and the environment produce outcomes that are not directly related to the features of the constituents. In this case, the study of the interface allows to investigate the complexity of the system (for further details on the concept of interface, see paragraph 4, 8 and 9).

Figure 3. The key role of the interface in controlling a system facing environment challenges. To achieve a goal, a system faces the environment that, in turn, challenges the system via

its interface. Since the system has to coordinate as a whole to make its interface effective to face environment, the interface constraints, and thus controls the system. **(a)** As an example, in a relatively complex system as a car, the components at the interface with the environment -- i.e. the steering wheel, the gas pedal, the brake -- allow for its full control. **(b)** Behavior, which is the interface between the central nervous system and the environment, controls the brain because the latter is constrained by the features of the behavioral responses to face the environment. **(c)** Similar theoretical framework can be applied to any system that faces the environment, as the immune system. See text for further details.

Figure 4. The relevance of behavior as interface has emerged during evolution. Environmental challenges have selected specific behavioral responses that, in turn, constrained and shaped brain activity. As a result, the brain produces these behavioral responses able to face the environmental challenges. This process has risen and defined the key role of behavior as interface between the environment and the brain. The information defining the how the central nervous system works goes from the environment to the brain via the behavior.

Figure 5. How to modify behavioral outcome: causal relationships between the environment, behavior and the brain. Along the evolutionary process, the environment shaped defined and well-orchestrated behavioral responses able to face its challenges. By contrast, no single or group of neural elements has been selected to be the sole orchestrator of complex behaviors. Consequently, despite neural elements as a whole allow the behavior to occur, the environment has a primacy in defining and driving behavioral outcome (see text for further details).

Figure 6. Interfaces are characterized by a simplified complexity. Interfaces are the place where systems interact with each other. Interfaces are characterized by a simplified complexity because they evolved for an effective communication and interplay between complex systems. This characteristic makes the study of interfaces a unique starting point to tackle and understand complex systems and their

emergent properties. Thus, the study of behavior, which is the interface between the brain and the environment, represents a compelling approach to address the complexity of the central nervous system.

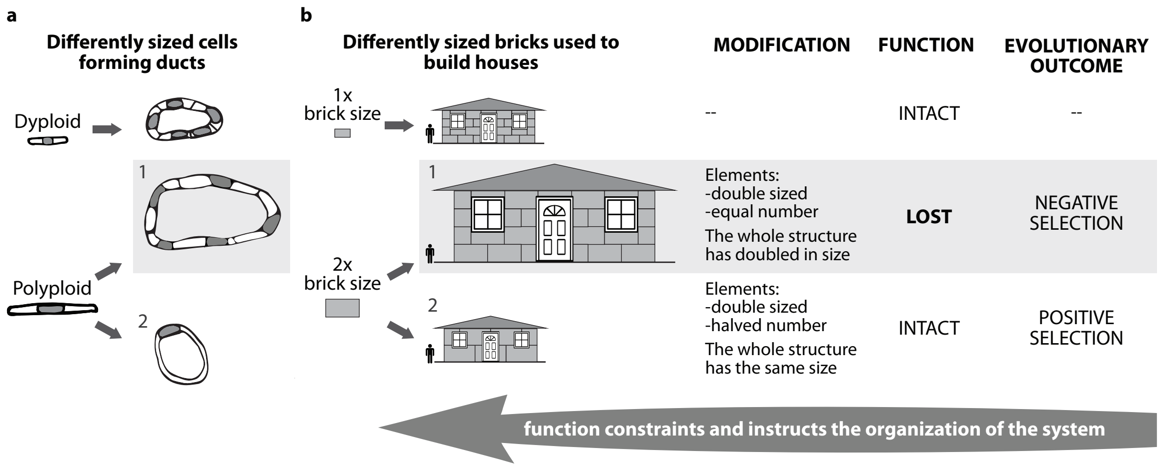
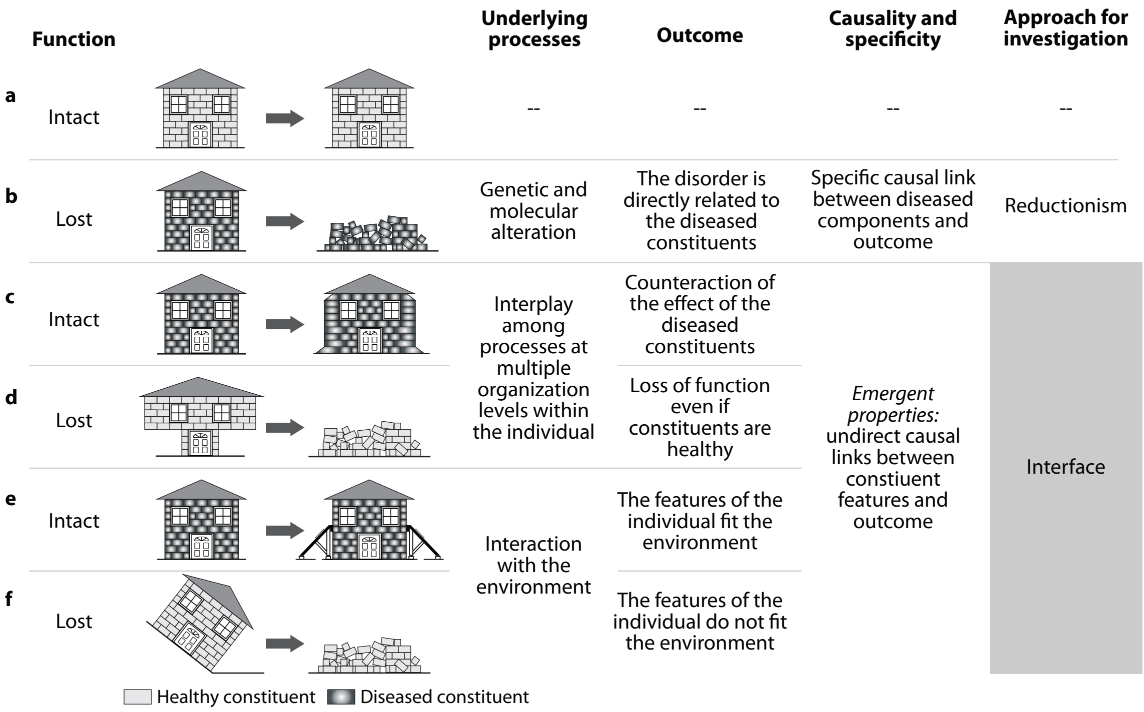

a
Differently sized cells forming ducts
Dyploid
1
Polyploid
2
b
Differently sized bricks used to build houses
1x brick size
2x brick size
1
2
MODIFICATION
FUNCTION
EVOLUTIONARY OUTCOME
--
INTACT
--
Elements:
-double sized
-equal number
The whole structure has doubled in size
LOST
NEGATIVE SELECTION
Elements:
-double sized
-halved number
The whole structure has the same size
INTACT
POSITIVE SELECTION
function constraints and instructs the organization of the system

Figure 1



Function
Underlying processes
Outcome
Causality and specificity
Approach for investigation
a
Intact
--
--
--
--
b
Lost
Genetic and molecular alteration
The disorder is directly related to the diseased constituents
Specific causal link between diseased components and outcome
Reductionism
c
Intact
Interplay among processes at multiple organization levels within the individual
Counteraction of the effect of the diseased constituents
d
Lost
Loss of function even if constituents are healthy
Emergent properties: undirect causal links between constiuent features and outcome
Interface
e
Intact
Interaction with the environment
The features of the individual fit the environment
f
Lost
The features of the individual do not fit the environment
Healthy constituent
Diseased constituent

Figure 2

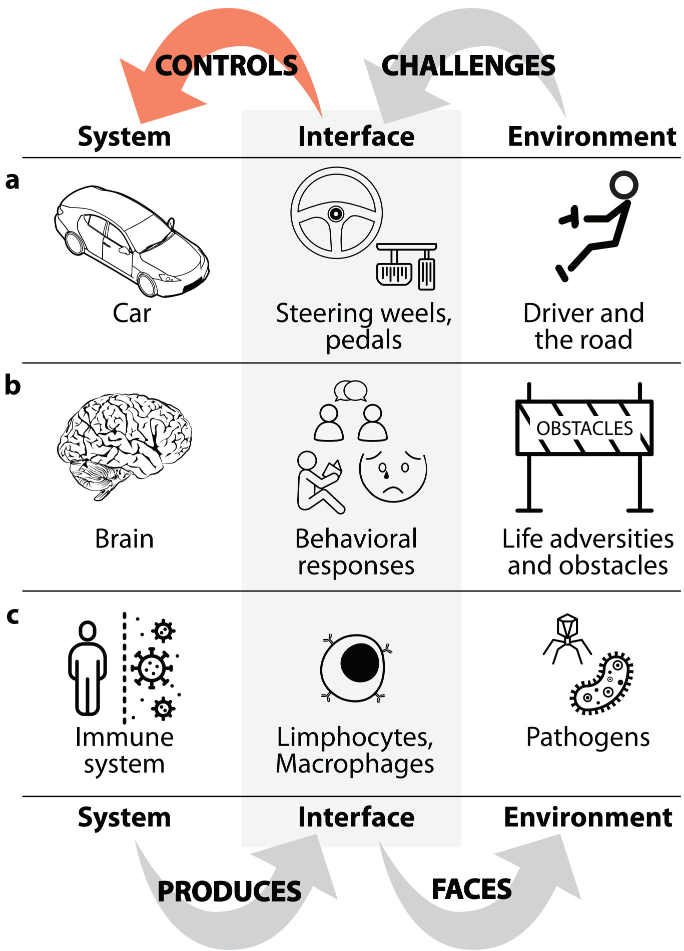

CONTROLS
CHALLENGES
System
Interface
Environment
a
Car
Steering weels, pedals
Driver and the road
b
Brain
Behavioral responses
OBSTACLES
Life adversities and obstacles
c
Immune system
Limphocytes, Macrophages
Pathogens
System
Interface
Environment
PRODUCES
FACES

Figure 3

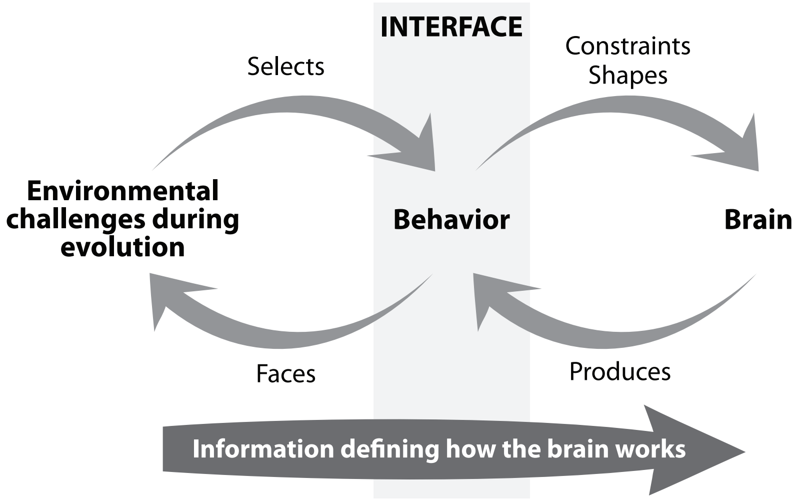

INTERFACE
Selects
Constraints
Shapes
Environmental challenges during evolution
Behavior
Brain
Faces
Produces
Information defining how the brain works

Figure 4

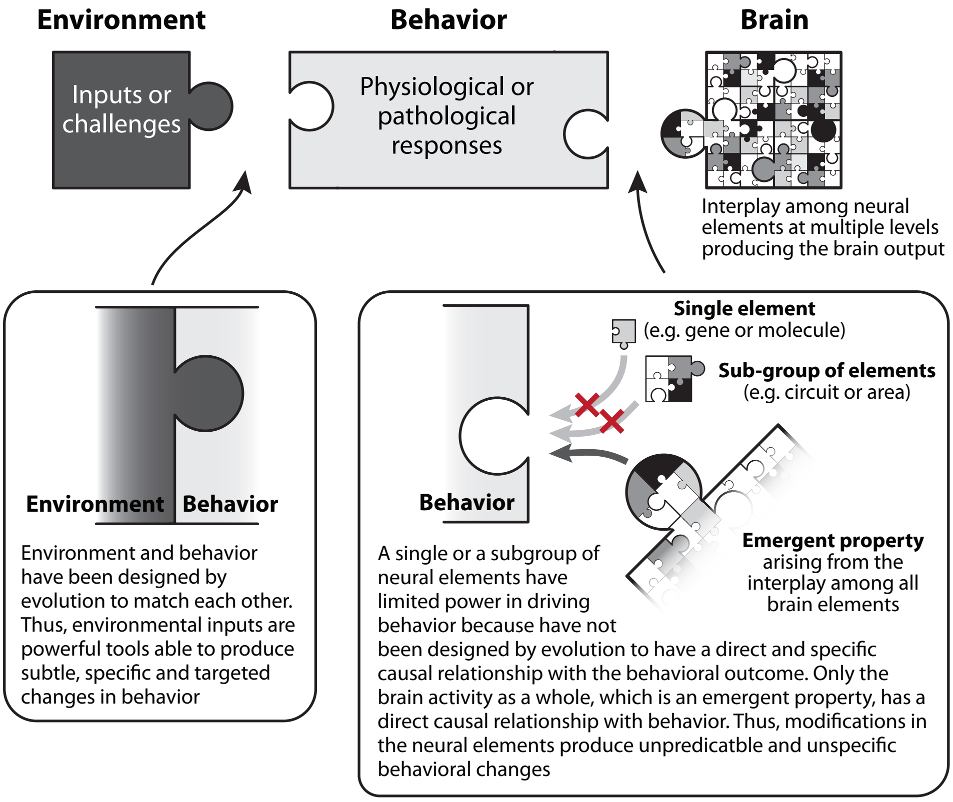

Environment
Behavior
Brain
Inputs or challenges
Physiological or pathological responses
Interplay among neural elements at multiple levels producing the brain output
Environment
Behavior
Environment and behavior have been designed by evolution to match each other. Thus, environmental inputs are powerful tools able to produce subtle, specific and targeted changes in behavior
Single element
(e.g. gene or molecule)
Sub-group of elements
(e.g. circuit or area)
Behavior
Emergent property
arising from the interplay among all brain elements
A single or a subgroup of neural elements have limited power in driving behavior because have not been designed by evolution to have a direct and specific causal relationship with the behavioral outcome. Only the brain activity as a whole, which is an emergent property, has a direct causal relationship with behavior. Thus, modifications in the neural elements produce unpredicatble and unspecific behavioral changes

Figure 5

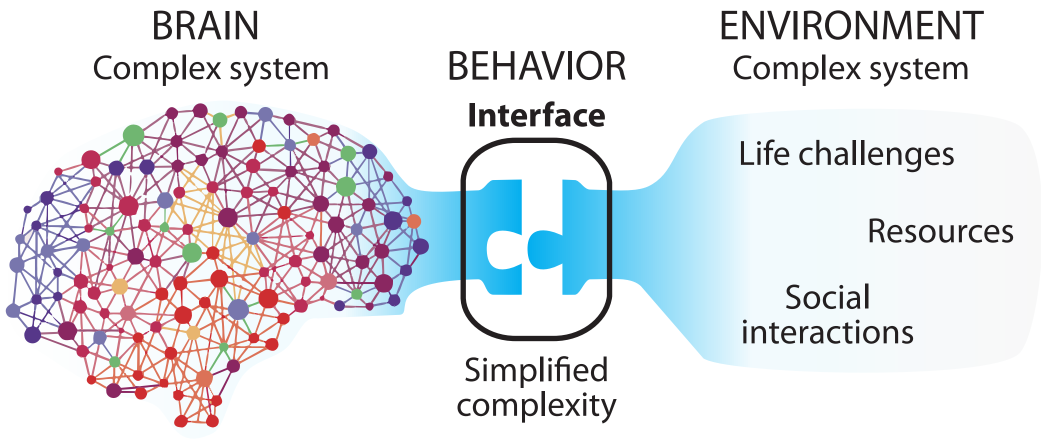

BRAIN
Complex system
BEHAVIOR
Interface
Simplified
complexity
ENVIRONMENT
Complex system
Life challenges
Resources
Social
interactions

Figure 6