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The Relevance of a Philosophical Toolkit to Advance Neuroscience

Uncovering the determinants of brain functioning, behavior and their interplay in the light of context

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Abstract

Notwithstanding the huge progress in molecular and cellular neuroscience, our ability to understand the brain and develop effective treatments promoting mental health is still limited. This can be partially ascribed to the reductionist, deterministic and mechanistic approaches in neuroscience that struggle with the complexity of the central nervous system. Here, I introduce the *Context theory of constrained systems* proposing a novel role of contextual factors and genetic, molecular and neural substrates in determining brain functioning and behavior. This theory entails key conceptual implications. First, context is the main driver of behavior and mental states. Second, substrates, from genes to brain areas, have no direct causal link to complex behavioral responses as they can be combined in multiple ways to produce the same response and different responses can impinge on the same substrates. Third, context and biological substrates play distinct roles in determining behavior: context drives behavior, substrates constrain the behavioral repertoire that can be implemented. Fourth, since behavior is the interface between the central nervous system and the environment, it is a privileged level of control and orchestration of brain functioning. Such implications are illustrated through the *Kitchen* metaphor of the brain. This theoretical framework calls for the revision of key concepts in neuroscience and psychiatry, including causality, specificity and individuality. Moreover, at the clinical level, it proposes treatments inducing behavioral changes through contextual interventions as having the highest impact to reorganize the complexity of the human mind and to achieve a long-lasting improvement in mental health.

KEYWORDS

complexity, context theory of constrained systems, interface, kitchen metaphor, reductionism

Abbreviations: 5HTTLPR, Serotonin-Transporter-Linked Promoter Region; RDoC, Research Domain Criteria.

1 | INTRODUCTION

The role of context in neuroscience and psychiatry has been largely overlooked till relatively recent times because of the opposing cultural influence of biological and genetic determinism (Comfort, 2018; Plomin, 2019) and the methodological limitations in quantifying brain changes induced by experiences. However, in the middle of last century, a number of key experiments and observations made its relevance began to emerge. Donald Hebb anecdotally reported that exposure to a complex environment improves behavioral capabilities in problem-solving tasks (Hebb, 1947). Hubel and Wiesel demonstrated the dramatic consequences of early sensory deprivation on the anatomy and physiology of the visual cortex (Wiesel & Hubel, 1963). The elegant studies by Rosenzweig and collaborators proved the influence of the environment as a testable scientific variable and showed that the quality of living conditions shapes brain and behavior at multiple levels, from morphology to chemistry (Rosenzweig, 1966; van Praag et al., 2000). More recently, the key role of the individual's environment in shaping brain activity has been increasingly recognized, showing that living conditions produce pervasive effects on brain circuits and define mental health (Castegnetti et al., 2021, #9; Geng et al., 2021; Mason et al., 2017; Meyer-Lindenberg & Tost, 2012, South et al., 2018; Tost et al., 2019). The idea of the environment has further evolved into the broader concept of *context*, which involves both external and internal conditions (e.g., environmental setting and mindset), the latter being also dependent on the individual's personal history (Benedetti, 2008; Branchi, 2022b; Di Blasi et al., 2001; Gilbody et al., 2006; Woltmann et al., 2012). Despite various valuable attempts (Zimmermann et al., 2007), there is no universally accepted operational definition of context and significant variations exist across different disciplines. Here, context is defined as the individual's experience of the environment. Accordingly, it encompasses not only the unbiased features of an experience but also the personality and state of mind of the individual while exposed to that experience (Klandermans et al., 2010; Wallsten et al., 1999). In this perspective, context is routinely assessed in psychology and psychiatry via questionnaires and interviews (Danese & Widom, 2020; Fakhoury et al., 2002; Kim et al., 2016).

Most theoretical frameworks describing the impact of context on brain and behavior postulate contextual factors as critical for shifting across discrete functional states, such as from a healthy to a pathological condition. For instance, traumatic or adverse experiences during early life or at adulthood are interpreted as – all or none – brain functioning switches (Nutt & Malizia, 2004; Ressler et al., 2022). According to such a view, once the shift toward the pathological condition has occurred, the dysfunctional brain produces diseased behavioral outcomes according to a bottom-up process (e.g., upward causation). Consequently, the medical goal is to target brain functioning to make it shift back to a healthy status, restoring mental wellbeing. By contrast, the theoretical framework proposed here assumes that the context provides continuous and dynamic information that constantly orchestrates neural activity. Without such information, the central nervous system is not able to function properly, and mental health cannot be attained. As a consequence, studies focused on understanding the brain without accounting for the context are seen as offering limited insight and therapeutic strategies have to involve contextual factors to effectively and finely reorganize the complexity of the mind.

1.1 | Complex vs. non-complex: merits and limits of the reductionist approach

Considering Warren Weaver's view on complexity, three primary types of problems are identified (Weaver, 1948): (i) *problems of simplicity*, which involve pairs of variables exhibiting a linear relationship when all other variables are kept constant, (ii) *problems of disorganized complexity*, encompassing phenomena involving a very high number of variables that can be addressed with probability theory and statistical mechanics, and (iii) *problems of organized complexity* that exhibit elevated levels of uncertainty, unpredictability, and involve numerous interconnected factors, giving rise to emergent properties, feedback loops, and nonlinear interactions. Here, the term *complex* refers to Weaver's definition of organized complexity.

Complex systems cannot be effectively and exhaustively investigated with a reductionist approach because the latter does not allow us to appropriately frame and analyze their features. Notwithstanding, reductionism has been impressively productive and continues to deliver outstanding results in the biomedical field when dealing with non-complex (i.e., Weaver's problems of simplicity) biological and medical phenomena. These involve, for instance, dysfunctional gene expression or pathogens, such as in monogenic disorders or infections (Thanh Le et al., 2020; Ying et al., 2019). Moreover, methodological reductionism is key because it represents one of the most effective human approaches to explore the world (Beresford, 2010). Therefore, the merits and limits of reductionism are contingent upon the scientific problem to deal with, and no theoretical approach is inherently correct or incorrect. Non-complex-phenomena can be effectively dealt with a reductionist approach while complex ones require alternative theoretical frameworks, such as the one proposed here.

2 | CONTEXT THEORY OF CONSTRAINED SYSTEMS

2.1 | Metaphors of the brain

A metaphor denotes an object, process or idea that is used in place of another as an interpretative framework to formulate potential explanations of empirical data (Bailer-Jones, 2002; Hesse, 1966). Metaphors are powerful conceptual tools to advance science as they allow us to describe and summarize the core of a hypothesis. However, metaphors also impose unwanted and unexpected constraints that, while making some things clearly visible, may shield others from view.

Over the centuries, different metaphors have been used to describe how the human brain works and generates behavior and mental states. These metaphors have been based on the knowledge and technological advance of the time. In the XVIII century, the Danish anatomist Nicolas Steno was the first to propose that the brain works as a machine. However, at that time, machines used either hydraulic power or clockwork, and thus the brain was often viewed as a watch. In the XIX century, with the discovery of electricity and that nerves respond to electrical stimulation, the brain was seen as a telegraph or a phone line. Nowadays, the most commonly used metaphor for the brain is the computer, with its hardware and software standing in for the biological brain and the processes of the mind. All these metaphors, elegantly described in the book *The idea of the brain* by Matthew Cobb (Cobb, 2020), have been able to take more and more into account the complexity of the central nervous system. However, even the computer metaphor, which is among the most sophisticated ones, presents a number of limitations in describing the current knowledge on the interplay between brain and behavior (Jonas & Kording, 2017) and its usefulness is highly debated (Matassi & Martínez Serra, 2023).

Here, I introduce a new metaphor and theoretical framework that may serve as tools to advance the understanding of the determinants of brain functioning, behavior, and their interplay.

2.2 | The Kitchen metaphor

The *Kitchen* metaphor illustrates the determinants of brain functioning and behavior taking into account their dynamic and bidirectional interplay, and the key role of context. In this metaphor, the brain is the kitchen, the biological elements – from genes, molecules to neural substrates – are the ingredients and tools available in the kitchen, and behavior and the associated mental states are the meal, that is, the ultimate output of the cooking process. Finally, the context is the circumstances in which the meal is prepared, such as being tired and alone, having invited in-laws, or cooking to achieve a favorable review by food critics (Figure 1). In this metaphor, the chef is merely one of the many elements contributing to the cooking process. Thus, it should not be seen as a deus ex machina but, akin to all the other elements in the kitchen, it plays a role in producing the outcome (e.g., meal).

It is worth noting that the metaphor should entail the organism as the kitchen because the whole organism contributes to the production of behavior. However, for the sake of simplicity, I am here considering only the brain as the kitchen.

1. At first sight and in line with a reductionist and deterministic approach, the meal (i.e., behavior) might appear as a direct outcome of the available ingredients (i.e., brain areas, neurons, molecules, and genes). However, this is not the case. For instance, the kitchen may contain exclusive and expensive ingredients, but it is the circumstances (i.e., context) that define if and how these ingredients are used. For instance, if a person is feeling fed-up, tired, and alone, even if the finest ingredients are available, these are unlikely to be used, but a simple and easy meal will be prepared. By contrast, if special circumstances occur (e.g., food critics' evaluation), the best ingredients among those available will be used. The availability of specific ingredients does not entail their use. By contrast, the recipe and thus the ingredients to be used are determined by the circumstances.

Conceptual implication: *context is the grand master: the circumstances define which behavioral responses are to be produced and these, in turn, recruit the neural, molecular, and genetic substrates that serve those responses* (see Section 3).

2. There is no direct and univocal match between the ingredients used and the meal to be cooked. The same ingredients can be used according to different recipes, and meals with overlapping features can be cooked using very different ingredients.

Conceptual implication: *substrates, such as genes, neurons or brain areas, do not directly relate to a specific behavioral*

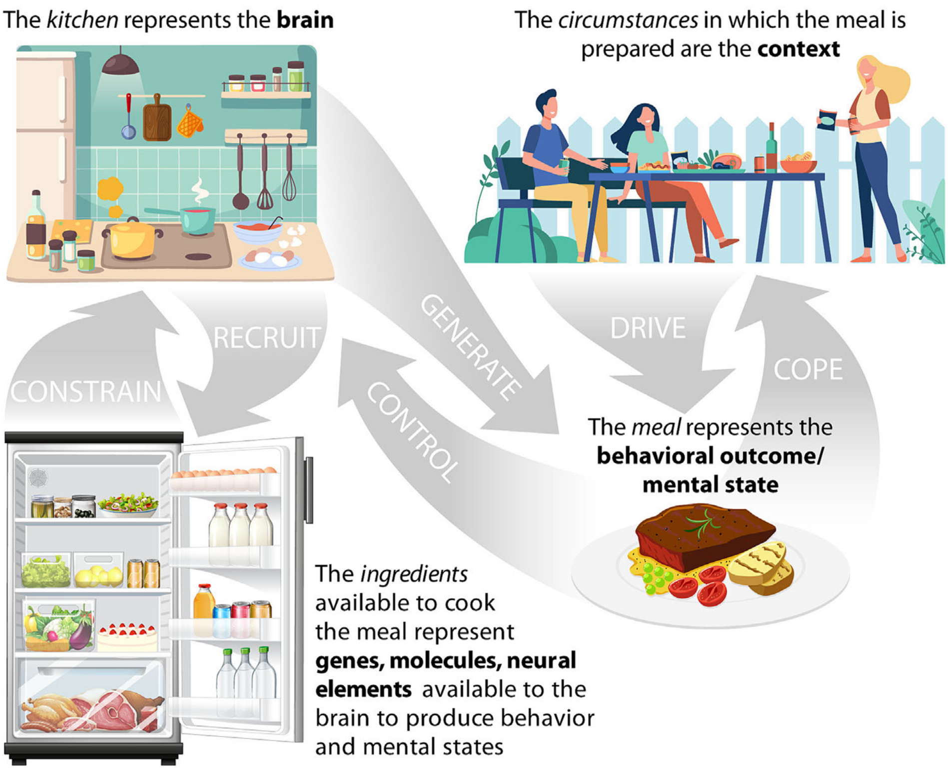

FIGURE 1 **The *Kitchen* metaphor.** The metaphor aims at uncovering the determinants of behavior, brain functioning and their interplay. While the brain (i.e., the kitchen) generates behavior (i.e., the meal), it is the context (i.e., the circumstances) that acts as the driver because contextual factors determine the behavioral responses to be performed (e.g., the meal to be cooked). The genetic, molecular and neural substrates (i.e., the ingredients available in the kitchen) constrain brain functioning and behavior by defining the repertoire of brain activities, and thus of behavioral responses (i.e., the meal recipe), that can be generated to cope with the context. See text for further details.

response as they can be combined in multiple ways to produce the same response or different responses can impinge on distinct genetic, molecular, neural substrates: relata do not precede relations. *This view, named* multiple realizability *(*Fodor, 1974; Putnam, 1967*), suggests to reconsider key concepts in the biomedical field as specificity and individuality* (see Section 4).

3. Both circumstances (i.e., context) and ingredients (i.e., substrates from genes to brain areas) are key in determining the quality of the meal (i.e., behavior). However, their role is antithetical: the circumstances actively determine the meal planning, while the available ingredients passively constrain its implementation. In other words, the available ingredients are affordances (see Section 6) as they determine which meal can be afforded to cope with the circumstances.

Conceptual implication: *context and biological substrates play diffeent roles in determining behavior. The context determines which behavioral responses to implement, while the molecular or neural substrates constrain the responses that can be implemented. For instance, while a threatening stimulus, such as a predator, triggers a behavioral response (*e.g., *fight or flight), the genetic, molecular and neural substrates available to the individual (*e.g. *the molecular machinery organizing the response to stress, the neural substrates of reflexes*, etc.*) determine which response can be finally afforded, even if this may not be the most effective* (see Section 7).

4. The meal (i.e., behavior) is the cornerstone. This is because it is the *interface* between the kitchen (i.e., the brain) and the circumstances (i.e., the context). Consequently, it stands as the only relevant factor in such interplay. For instance, the quality of the meal is almost the sole determinant of a favorable review by food critics. By contrast, the ingredients, though crucial in determining the meal quality, lack a direct relationship with the meal (because of multiple realizability) and with addressing the circumstances.

Since the meal is the cornerstone, the entire cooking process is aimed at achieving the meal and the ingredients are selected accordingly. Therefore, it is the meal (i.e., behavior) that controls the ingredients (i.e., genes, molecules, neural substrates) and not vice versa.

Conceptual implication: *in any system, the interface is a key regulator of the system organization (*Branchi, 2022b*). As behavior and the associated mental states are the interface between the central nervous system and the living environment, behavior is a privileged level of control and orchestration of brain structure and activity, with a unique capability to reorganize the complexity of the human mind* (see Section 8).

Considering the critical role of the context and of the constituents (e.g., the genetic, molecular and neural

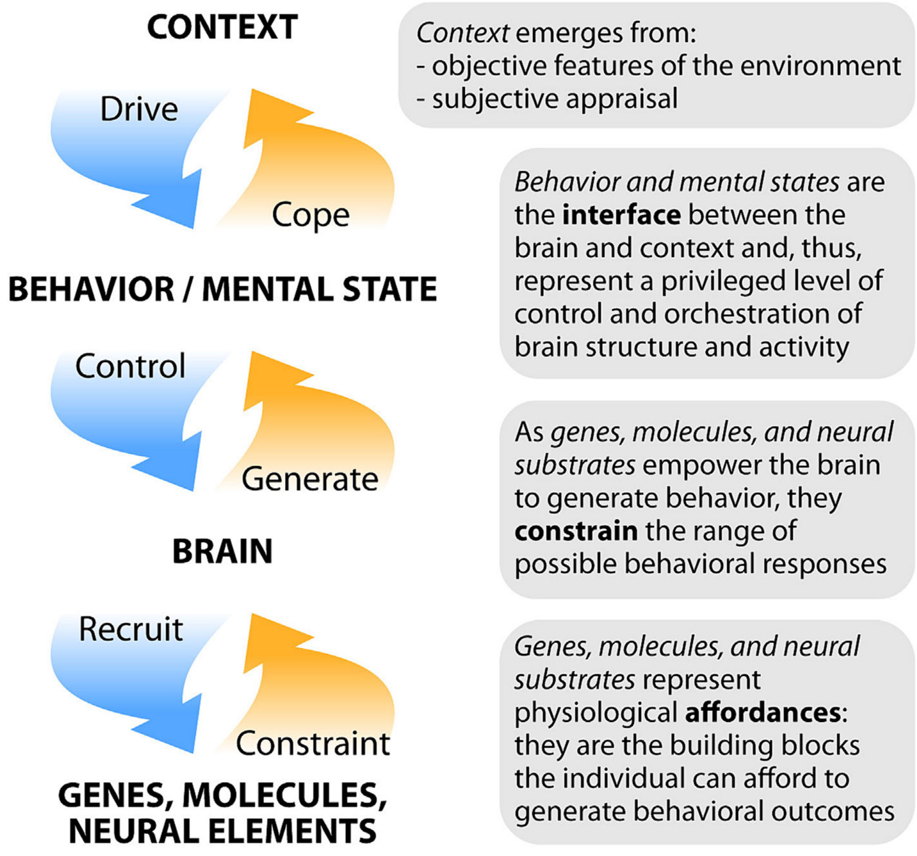

FIGURE 2 **The interplay between context, behavior, brain, and genetic, molecular and neural substrates.** The *Context theory of constrained systems* predicts the role and the interplay among the different players involved in brain functioning and behavior. Context, which emerges from both the objective features and the subjective appraisal of the environment, drives behavior by compelling specific behavioral responses that can cope with its challenges. In turn, behavior controls brain functioning because the latter has to generate behavioral responses that effectively address the context. Moreover, the brain recruit genes, molecules and neural substrates required to produce the neural activity underlying the required behavioral responses. Finally, the substrates constrain brain functioning – and thus behavior – because they limit the repertoire of behavioral responses that can be generated. See text for further details.

substrates) in, respectively, driving and constraining the structure and activity of a system (i.e., the brain), the theoretical framework that underlies the *Kitchen* metaphor has been named the *Context theory of constrained systems*. I now elaborate on its implications, describe the supporting results, and discuss the formal tools it provides to uncover the determinants of brain functioning, behavior and their interplay.

3 | CONTEXT IS THE GRAND MASTER DRIVING BEHAVIOR AND NEURAL ACTIVITY

3.1 | Context gives meaning to biological processes, from genetic expression to behavior

> *Without context, words and actions have no meaning at all. This is true not only of human communication in words but also of all communication whatsoever, of all mental process, of all mind, including that which tells the sea anemone how to grow and the amoeba what he should do next* (Bateson, 1988).

As clearly depicted by Gregory Bateson, context is the *ensemble* of those circumstances that form the setting for an action or process and gives meaning to any action or process. Accordingly, the same action or process, under different circumstances, can lead to clearly distinct outcomes. Consequently, context drives behavior, triggering responses that are meaningful to cope with its challenges: behavioral responses must match the context to be effective in achieving the individual's goals. Behavior, in turn, controls brain functioning, making it generate those responses that are meaningful for the context. Finally, the brain recruits the neural, molecular and genetic substrates that serve it. Therefore, the context is the grand master giving meaning to biological processes at all organizational levels of the organism (Figure 2). In addition, since the context goes through constant changes, its action is dynamic and continuous.

The view of context as the main organizer of the organism, from the behavioral to the genetic level, is grounded in the *downward causation model* (Campbell, 1974; Ellis, 2019; Noble, 2012), by which functional constraints at high scales define the processes occurring at lower scales. A telling example of downward causation is provided by the seminal work of the German embryologist Gerhard Fankhauser on the protonephron (i.e., kidney-like organ) of the newt *Notophthalmus* *viridescens* larvae (Fankhauser, 1945; Uversky & Giuliani, 2021). This species goes through spontaneous polyploidization (i.e., modification of the number of sets of chromosomes). The different polyploidy does not affect the individual health status and fitness but affects the size of the cells the individuals are made up of (e.g., polyploid cells are almost double sized compared with diploid cells). Fankhauser found out that all individuals, despite the difference in their cell size, have overlapping organ size and structure. To achieve this, individuals with larger cells had organs and structures made up by a reduced number of cells and vice versa. In particular, protonephron from polypoid individuals are made up by around half the number of cells of those from diploid individuals. The preservation of protonephron structure and size is because of the need to keep their function—that is key for life – which, in turn, is determined by contextual factors as the properties of fluids. Overall, it is the function of a biological process, and therefore the context in which the process takes place, that drives and organizes the biological structure (Noble et al., 2019). Fankhauser's seminal work is an elegant and effective example of downward causation urging the study of molecular or cellular processes considering how the whole phenomenon is organized and how it behaves when embedded in its context (Branchi, 2022b; Kim, 1999).

An increasing number of studies are demonstrating the downward causation, and thus the role of context, in defining the outcome of biological processes at all levels of the organism organization. For instance, the complete deletion of up to 80% of genes in yeast has no obvious phenotypic consequence in a rich medium. However, when the environmental context is modified, e.g., by reducing the availability of resources, the function of the deleted genes for yeast survival emerges (Hillenmeyer et al., 2008). Thus, the context determines the consequences of gene modifications. Similarly, it has been reported that, in mice living in standard laboratory conditions, the deletion of specific genes has no effect or can even be advantageous. However, in challenging conditions such as the mouse natural environment, the same gene deletions lead to a significant reduction in the survival rate (Giorgio et al., 2012).

Complex behavioral responses and their underlying neural substrates can also be fully understood only when the context is considered (Lipp & Wolfer, 2013). As an example, in laboratory settings, the deletion of the gene coding for the brain cytoplasmic (BC1) RNA, a small non-coding RNA present in the dendritic microdomains of neurons, leads to behavioral changes interpreted as beneficial, such as a modification of the fear response (Lewejohann et al., 2004). However, the same gene deletion in naturalistic conditions is dysfunctional (Lipp & Wolfer, 2013). Likewise, the deletion in mice of the tropomyosin receptor kinase B (trkB) for neurotrophins produced alterations in behavioral flexibility that could be identified only in naturalistic settings (Vyssotski et al., 2002).

It is interesting to note that the concept of context can be applied at different scales. Not only the context of the whole organism is crucial in defining its function and structure, but the specific context at any level of the organism organization drives and orchestrates the processes occurring at that specific level. For instance, the neuronal responses of a single olfactory cell is dependent on the context of the internal state of the functional assembly to which the cell participates (Bargmann, 2012; Niell & Stryker, 2010; Zagha & McCormick, 2014), and the functional role of a brain area is contingent on the status of other connected areas (McIntosh, 2004). Furthermore, it has been shown that neurons 'tune' themselves to achieve functional interplays that are consistent with a given target function according to a downward causation process (Alonso & Marder, 2019; Marder & Prinz, 2002; Marder & Taylor, 2011; Prinz et al., 2004). As a final and striking example, in fish, when the nucleus of one species is taken and inserted into the denucleated but fertilized egg cell of a different species, the manipulated egg develops into an adult phenotype with features intermediate between the two original species, demonstrating the context provided by the elements in the egg cytoplasm organize the action of the genes (Sun et al., 2005; Sun & Zhu, 2014).

3.2 | Context makes the effect: placebo response

Probably, one of the most compelling examples illustrating the essential role of context in driving the organization of biological processes is the placebo effect, which occurs following the administration of an inert treatment, named placebo, given along with verbal suggestions of clinical improvement thereby making the patient believe that the treatment is real and effective (Benedetti, 2008). The patient's expectation of clinical benefit is critical (Andrews, 2001; Bargmann, 2012) and this is highly dependent on the therapeutic context (e.g., the sight of a syringe) that anticipates the benefit (Colloca & Benedetti, 2005). Thus, the placebo effect is a biological phenomenon that emerges from the individual's psychosocial and emotional context (Benedetti, 2008). It is very important to highlight that the placebo effect is not just in the individual's mind and does not affect only behavior but it can be detected and measured as changes in

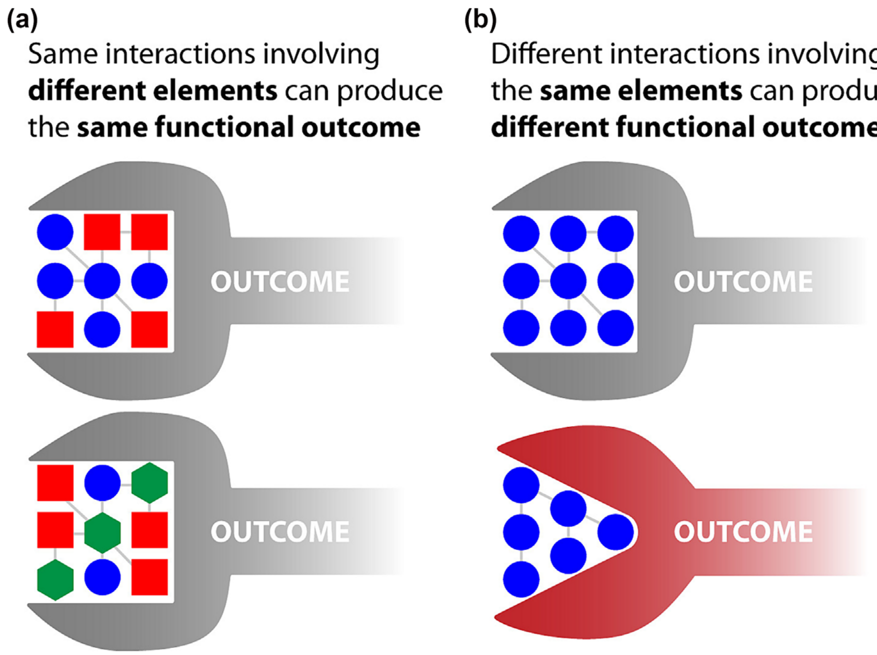

FIGURE 3 **Relata do not precede relations.** In complex systems, such as the brain, the outcome results from the relationship among the elements. Therefore, elements, such as genes, neurons or brain areas, do not directly relate to specific behavioral responses. (a) They can be combined in multiple ways to produce the same response or (b) different responses can impinge on the same elements.

molecular markers and physiological processes (Benedetti et al., 2005; Zunhammer et al., 2021). Among the most important example of placebo effect is pain perception that is highly modulated by emotional context and expectations (Price et al., 1999; Swerts et al., 2022). In the psychiatry field, evidence of significant rates of placebo responses has been found in antidepressant trials (Cipriani et al., 2009; Kirsch et al., 2008; Stone et al., 2022; Walsh et al., 2002). It is highly important that also in these trials the effects of the placebo have been documented at a biological level as well. In particular, in a placebo-controlled study, patients receiving the SSRI fluoxetine and those receiving placebo showed anatomically overlapping metabolic changes in position emission tomography scans, which were associated with the clinical response (Mayberg et al., 2002).

4 | NEURAL SUBSTRATES DO NOT MATCH BEHAVIORAL RESPONSES

One of the key conceptual implications of the *Context theory of constrained systems*, which is illustrated by the *Kitchen* metaphor, is that different combinations of elements at low organizational level (i.e., ingredients) can achieve the same goal at higher organizational level (i.e., the meal) and vice versa (Figure 3). In other words, different genes, molecules or neural substrates can produce the same behavioral response and/or mind state and different responses can impinge on the same substrates. This implication overlaps, at least in part, with the hypothesis of *multiple realizability* described by the philosophers of mind as Hilary Putnam (Putnam, 1967) and Jerry Fodor (Fodor, 1974) and, later, David Marr (Marr, 1982). Furthermore, the impracticability of matching substrates with complex behavioral responses arises also by acknowledging behavior as an emergent property that, by definition, cannot be explained, or even predicted, by studying its individual constituents (Van Regenmortel, 2004). In other words, none of the constituents summarize or have a direct causal or specific relation with the emergent property. These issues urge to revisit the concept of *specificity* in the applied neuroscience field and in the biomedical sciences in general.

4.1 | Revisiting the concept of specificity

No or very limited univocal relations exist between specific genetic, molecular or neural substrates and complex behavioral outcomes or mind states. This is supported by different lines of evidence. First, the same change in behavior and/or mind state, such as the recovery from psychopathology, can be accompanied by different neural rearrangements. Neuroimaging studies show that therapeutic strategies can produce their beneficial effects not just normalizing altered brain activity patterns but by recruiting areas not previously activated (Beutel et al., 2010; Prasko et al., 2004; Sakai et al., 2006). In addition, the same experiences can lead to different modifications in brain functioning across individuals (Apostolova et al., 2010; Nakao et al., 2005) according to their personal history and biological background (Cassiers et al., 2018). Second, different activation patterns of brain elements can produce the same overall response. For instance, widely disparate sets of neural mechanisms lead to virtually indistinguishable network activities even in very simple networks such as the pyloric network of the crustacean stomato-gastric ganglion. This points out that many different combinations of neural properties, such as synaptic strengths and neuronal features, are consistent with a proper and overlapping network activity (De Schutter et al., 2005; Edelman & Gally, 2001; Gutierrez & Marder, 2014; Marder & Goaillard, 2006; Prinz et al., 2004). Third, the same group of neural substrates can switch among different interaction patterns producing radically different behavioral outcomes (Sakurai & Katz, 2017; Takemura et al., 2017). Overall, these findings indicate the impossibility of unequivocally mapping complex behavior and mind states on the specific state of the dynamic features of the neural substrates.

A very important consequence of the lack of specificity between the elements and the outcome of a complex system, such as the brain, is the unlikelihood of controlling its outcome by targeting a single or a subgroup of elements. This is in line with the variability of the effects of the manipulation of genes or pathways across individuals (Olsen et al., 2013) and with the impact of contextual factors in determining their outcome (Hillenmeyer et al., 2008; Lipp & Wolfer, 2013). Further evidence is provided by the lack of prospective molecular or genetic markers for mental illnesses, such as major depressive disorders (Carvalho et al., 2020; Kennis et al., 2020; Winter et al., 2022). Therefore, the regulation of behavioral responses and mental states does not reside in any specific neural substrate but arises from the interplay among all the neural substrates involved.

One of the most striking examples of the epistemological difficulty in establishing specificity in the relationship between neural substrates and behavioral outcome concerns a relatively simple organism such as the roundworm (*Caenorhabditis elegans*). The full description of its genome, cell types and interaction diagram in its extremely simple brain comprising only 302 neurons (Bargmann, 1998) is not enough to explain and predict the behavior of this worm, further highlighting how arduous is to infer behavior from neural substrates (Badre et al., 2015; Cooper & Peebles, 2015; Gomez-Marin et al., 2014; Krakauer et al., 2017). This is in line with theoretical studies showing that approaches based on the analysis of single or subgroups of neural substrates have limited power for the understanding of the overall outcome of the central nervous system (Jonas & Kording, 2017). This limitation is not contingent upon the number of elements comprising the system but rather linked to the system quality and applies to all complex systems (Weaver, 1948).

4.2 | Emergence of individuality

Since there is no single match between genetic, molecular and neural substrates and behavioral outcome, each individual implements distinct and unique combinations of substrates to generate the same behavioral responses. These combinations are determined by their personal history and biological features (Clarke, 2013). Therefore, no two brains are identical in their organization, bestowing individuality. This is demonstrated by the important differences across individuals in the parameters defining even the simplest neural function (Edelman & Gally, 2001; Gunaratne et al., 2017; Marder et al., 2022; Prinz et al., 2004; Zhang et al., 2020). This view holds highly relevant implications for neuroscience. First, it is unlikely to identify overlapping sets of substrates underlying even the most tightly regulated brain and behavioral functions across individuals. Second, in order to advance the capability to understand the brain, interindividual variability should be acknowledged as an essential organizational feature of the nervous system and not as 'experimental noise' (Prinz et al., 2004). Third, the likelihood of unraveling the substrates of behavior is higher when investigating a single individual than a group.

4.3 | Implications of individuality and multiple realizability for neuroscience

A critical implication of individuality – and thus of multiple realizability – is the lack of explanatory power of reductionism when dealing with complex systems such as the brain and behavior: since the same behavioral response and mental state can be generated by different brain substrates and vice versa, it is no possible to unambiguously match the two levels. This argument has been used against reductionism since the second half of last century (Fodor, 1974; Marr, 1982). In response to this, it is often proposed that the huge technical progress occurring in recent years, and the consequent increasing amount of details about the neural mechanisms, will overcome this issue and lead to mapping behavior on specific brain substrates (Robie et al., 2017; Siddiqi et al., 2022). However, this approach appears not able to solve the limitations of reductionism because even the most detailed description of the central nervous system cannot be generalized across individuals (Prinz et al., 2004). In addition, a direct link between neural mechanisms and behavior appears to be not possible because, as mentioned above, complex systems, including the central nervous system, are characterized by recurrence, feedback, degeneracy, interdependency and emergence to a degree that makes localization of function not meaningful (Anderson, 1972; Chan et al., 2014; Edelman & Gally, 2001; Fregnac, 2017).

Multiple realizability also points out the potential limitations of initiatives as the Research Domain Criteria (RDoC), a recently proposed research framework to investigate the neural bases of mental disorders (Insel, 2014). Though RDoC correctly implies that behavioral and neural features are often cross-disorders and goes beyond the symptom-based diagnostic system, its attempt to link the neuropsychological dimensions to specific biological markers, from genetic to physiological ones, does not fit the lack of specificity and the emergent properties of complex systems as the brain. Accordingly, biological markers predictive of mental disorders, such as major depression, have not yet been identified and current results are not yet useful for clinical practice (Carvalho et al., 2020; Kennis et al., 2020; Stein et al., 2022).

4.4 | Localization of functions

It is worth noting that the theoretical framework proposed here aligns with the view of localization of biological/neural functions within specific brain areas or circuits (Burnston, 2016). The elements and regions within the central nervous system do have distinct functional roles, though there is a certain degree of overlap. For instance, it has been demonstrated that specific groups of neurons perform distinct computations, such as thresholding or filtering of signals (Carandini, 2012). However, it is unlikely to directly map these neural functions to distinct behavioral responses or mental states (Westlin et al., 2023), which emerge from the functioning of the entire brain (and the body). This view can again be illustrated exploiting the kitchen metaphor: the ingredients and tools used during the cooking process have definite functions. For instance, specific and clearly identifiable functions can be attributed to an ingredient such as butter or tools such as the whisk or the spoon. Nonetheless, in most cases, these functions do not directly map to the meal that has been cooked because the same ingredient or tool can be employed for various recipes, and alternative ingredients or tools can be utilized to achieve the same goal. Overall, functions are expected to be localized within system elements but, in most cases, they do not directly match the system outcome. Nonetheless, in line with the quote by Gregory Bateson that emphasizes the role of context in bestowing meaning upon processes (see Section 3.1), when contextual factors are considered, the ultimate outcome of a single or a subgroup of elements within the system becomes a considerably more reliable predictor of a specific system outcome. Accordingly, it has been proposed that function–structure mapping within the human brain is context-sensitive (Burnston, 2016; Viola, 2021).

5 | CONTEXT DRIVES TREATMENT OUTCOME: RETHINKING NEUROPSYCHOPHARMACOLOGY

As no or very limited one-to-one links between biological substrates and behavior exist in a complex system as a human being (Branchi, 2022b; Edelman & Gally, 2001; Prinz et al., 2004), the changes in neural activity triggered by psychiatric drugs are expected to be in most cases unable to produce univocal and distinct changes in behavior. Indeed, an increasing number of studies show that psychiatric drugs do not produce univocal outcomes but create the conditions favoring changes in behavioral outcomes and mental health, for instance allowing the transition from a pathological to a healthy state. However, it is the context that finally drives the outcome of such change (Carhart-Harris et al., 2018; Branchi & Giuliani, 2021; Bottemanne et al., 2022; Branchi, 2022b; a; Ford & Young, 2022; Price et al., 2022). The role of context as the main factor determining mental states and behavioral responses is particularly evident with psychiatric drugs that increase neural plasticity such as antidepressants. Plasticity is the capacity of the nervous system to modify its activity and structure in response to contextual factors (Branchi, 2011, 2022a; Delli Colli et al., 2024). Consequently, the outcome of these treatments depends on context and consists in the amplification of the impact of contextual factors 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; Viglione et al., 2019). Similar results have been found for other classes of antidepressants such as ketamine (Bottemanne et al., 2022; Price et al., 2022; Wilkinson et al., 2021) and psychedelics (Carhart-Harris et al., 2018), in addition to totally different classes of compounds such as oxytocin for the treatment of the autism spectrum disorder (Ford & Young, 2022).

Accordingly, the combination of psychotherapy with antidepressants has been shown to be more effective than the drug alone (Cuijpers et al., 2020). The key role of context is increasingly demonstrated also in studies concerning genetic polymorphisms affecting serotonin levels, such as the serotonin-transporter-linked promoter region (5HTTLPR) polymorphism, that makes individuals either more vulnerable or capable to recover from depression, according to their living conditions (Delli Colli et al., 2022). As a final telling example from rodent studies, a testosterone surge in the same individuals induces opposite behavioral outcomes according to social context, either facilitating prosocial responses if administered during affiliative encounters, or triggering aggression if administered during fights (Kelly et al., 2022). Overall, these studies emphasize the relevance of a precise/personalized medicine approach that takes into account contextual factors as main driver of brain functioning and behavior to finally develop reliable and effective treatments for psychiatric disorders.

6 | CAUSATION INSIDE AND OUTSIDE COMPLEX SYSTEMS: INSTRUCTIVE VS. PERMISSIVE CAUSALITY

The *Context theory of constrained systems* aligns with Denis Noble's view that "no privileged level of causation" exists in biology (Noble, 2012). This view posits that causation cannot be exclusively attributed to any level of organization of a complex system as a living being. Therefore, behavior is not caused at the molecular, cellular, or organismal level but it is simultaneously caused at all levels, and none of them is inherently more fundamental or privileged than the others. In other words, causation is distributed across multiple levels, and understanding it requires looking at the interactions and relationships between all the levels (Sapolsky & Balt, 1996). The theoretical framework proposed here extends Noble's view, establishing a distinction between causation inside and outside the system.

Causal relationships can be roughly classified into two main categories: instructive and permissive (Branchi & Giuliani, 2021). Instructive causality implies that an action directly determines the quality of its effect (e.g., via transfer of energy or information), whereas permissive causation influences the likelihood of an effect to take place. As an example, a dangerous stimulus, such as a predator, modifies behavior by prompting a flight response via instructive causality. Instead, the capability to detect danger affects behavior via permissive causality: the danger is present, but the behavioral response will depend on the awareness of its existence. These two types of causal relationship are differently relevant when investigating causation inside or outside a complex system, such as the brain.

The principle of complexity, where the *whole is more than the sum of its parts*, and its implications about causality apply to the elements inside but not to those outside a system. Indeed, a system can interact with the outside world, such as another system, in a linear and direct fashion. In the light of this distinction, the Noble's view (Noble, 2012) applies to the elements inside a complex system (e.g., genes, neural substrates) where no privileged level of instructive causality linking elements to the system outcome exists. Their modification does not compel the system toward a defined outcome, but these elements act as constraints establishing a permissive causal relationship with the outcome, thereby affecting the likelihood of its occurrence. In contrast, elements outside the system (i.e., contextual factors) can act via instructive causality, steering the system to a specific outcome. When applying this perspective to elucidate the determinants of brain functioning and behavior (Branchi & Giuliani, 2021), it follows that biological substrates affect behavior through permissive causality, while contextual factors can determine behavior through instructive causality (Figure 4a). It is noteworthy that context can operate also as through permissive causality, as environmental factors may limit the implementation of specific behavioral responses (Koops et al., 2014). This view of causality in complex systems can be illustrated with the *Kitchen metaphor*: no single ingredient or tool in the kitchen has an instructive causal power able to univocally determine the meal to be prepared, but they affect the cooking process via permissive causality (e.g., a given recipe cannot be cooked if an ingredient is missing). Conversely, the circumstances (e.g., the preferred meal of a friend who has been invited to join for dinner) will dictate which recipes are to be prepared via instructive causality.

7 | REINTERPRETING THE ROLE OF GENETIC, MOLECULAR AND NEURAL SUBSTRATES AS CONSTRAINING FACTORS

As demonstrated by a huge number of studies, biological elements such as genes, molecules and neural substrates, dramatically affect behavior. However, in line with the *Kitchen* metaphor and the different types of causal relationship described above (see Section 6), their role in determining behavior is antithetical to that of contextual factors. While *biological substrates constrain the*

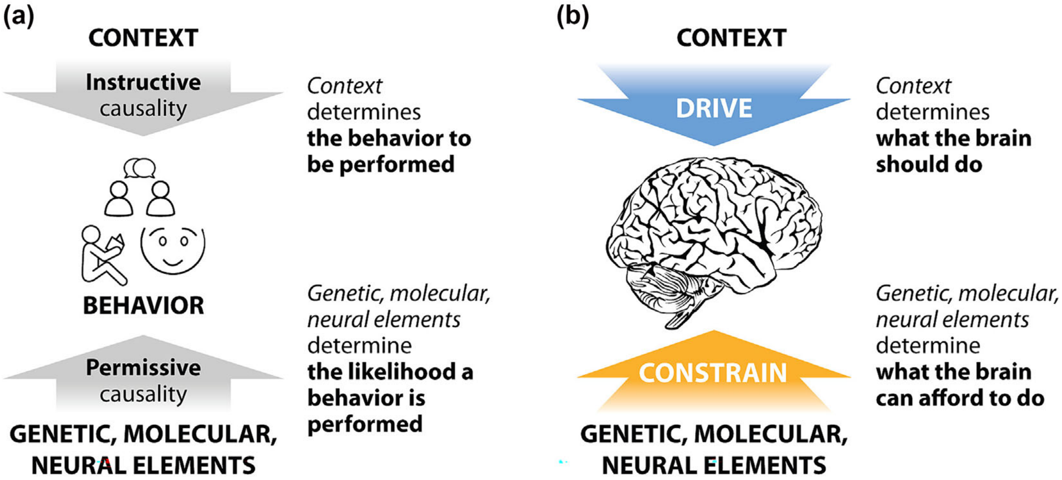

FIGURE 4 **The distinct roles of context and genetic, molecular and neural substrates in determining behavior and brain functioning**. (a) Context and substrates determine behavior according to two distinct types of causality: context operates through instructive causality, determining which behavioral response to perform to effectively address the contextual challenges. Whereas, substrates operate through permissive causality, determining the likelihood of a specific response by constraining the range of feasible responses. (b) Context determines which neural activities should be implemented to produce the effective behavior to address the contextual challenges. By contrast, substrates determine brain functioning by constraining the neural activities that can be afforded. Substrates therefore represent structural and functional affordances as they are the building blocks used to generate the behavioral response. See text for further details.

behavioral responses that can be afforded, context drives which behavior should be performed to cope with the contextual challenges (Figure 4b). Genes, molecules and neural elements indeed represent structural and functional *affordances* as they are the building blocks used to generate the behavioral response. The term *affordance* has been widely used in past (Gibson, 1979; Varela et al., 1991), however here it is reinterpreted to indicate the structures of usefulness or viability provided by the biological elements that constitute the individual. When a biological substrate at any level is missing or impaired, for instance because of genetic mutations or lesions, a behavioral response cannot be afforded anymore as the elements to generate it are no longer available. However, a response has still to be produced because of the need to cope with the context. Thus, an alternative response, which is affordable despite the missing substrate, is generated, even if its efficacy could be lower than the original one. Therefore, biological elements must be interpreted not as driving but as constraining factors in brain functioning and thus in the generation of behavior.

It is worth noting that the idea of genes as constraints aligns with the viewpoints put forward in the past in various fields. For instance, Susan Oyama in her classic work (Oyama, 2000) *Evolution's eye: A systems view of the biology-culture divide* suggested that (p. 54) "The other way of construing the genetic program is to declare that the genes determine the range of possibilities: they set the limits on development". Similarly, Ernst Mayr "claimed that "the range of possible variation is itself included in the specifications of the code" of the genetic program (Mayr, 1961).

8 | BEHAVIOR IS A PRIVILEGED LEVEL OF CONTROL OF NEURAL ACTIVITY: THE INTERFACE PRINCIPLE

When investigating the capacity of a complex system (e.g., the brain) to deal with the external world, information about the system internal organization (i.e. the substrates) is limitedly informative because, as mentioned earlier, multiple substrate organizations lead to the same outcome or the same organization can produce multiple outcomes (Prinz et al., 2004). By contrast, the *interface* of the system is highly relevant because it directly determines its success in coping with contextual challenges. As behavior is the interface between the brain and the environment (i.e. the context), it is the only cornerstone for the individual's success (Branchi, 2022b). As interface, behavior recruits the neural substrates that serve its implementation to cope with the context. Consequently, it is not the brain or neural substrates that define behavior but behavior defines which neural activity, and the associated genetic and molecular processes, will take place, according to a downward causation process (Ellis, 2019; Noble, 2012). Therefore, *behavior controls and orchestrates brain functioning* (Branchi, 2022b)

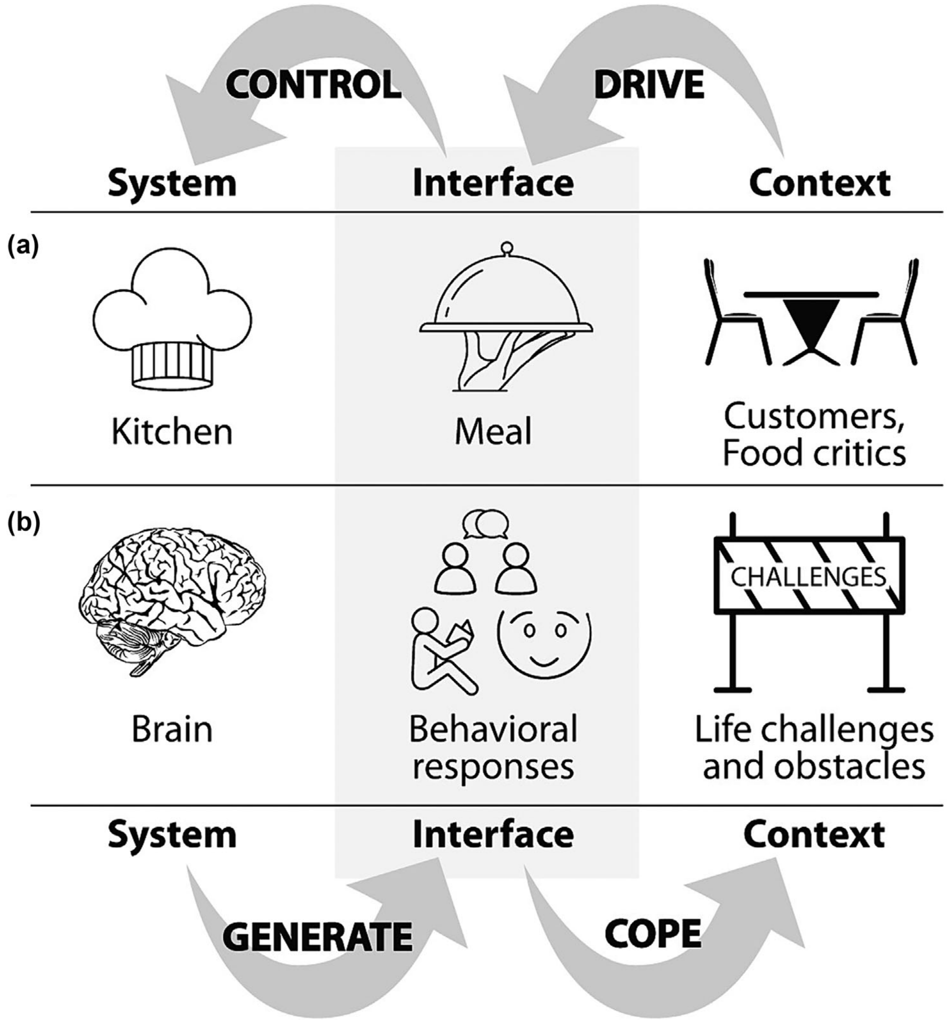

FIGURE 5 The key role of the interface in controlling the system. Contextual factors drive a system via its interface that, in turn, controls the system to generate the appropriate interface to cope with the context. (a) in the light of the kitchen metaphor, circumstances drive the meal, defining the receipt to be cooked that, in turn, controls the processes to be performed in the kitchen to generate the meal tailored to address those circumstances. Similarly, (b) behavior, as interface between the central nervous system and the context, is driven by the context. Concurrently, behavior controls the brain that, in turn, generates the responses required to cope with contextual factors. Adapted from Branchi, 2022b.

(Figure 5). Such a statement may appear as a paradox because the brain is there to generate behavior. However, the two processes occur in parallel without contradictions: behavior controls neural activity while the latter generates it. Exploiting the *Kitchen* metaphor, the meal to be cooked defines which ingredients are to be used, but it is the ingredients to generate the meal. This conceptual approach, named the *interface principle*, has been thoroughly discussed in a recent review article (Branchi, 2022b).

8.1 | Shared patterns across individuals at the interface: taming interindividual variability

The interface (e.g., behavior) represents the level of organization of a complex system where interindividual variability is expected to be the lowest. This is because the interface is where the system structure and activity are highly organized for effective interplay and coping with the external world (Branchi, 2022b). For instance, when investigating the pyloric network of the crustacean stomato-gastric ganglion as a system, its interface – i.e. the production of pyloric rhythms – is highly conserved across individuals because it is constrained by its function in the digestion of food. By contrast, lower organizational levels imply a greater interindividual variability that increases with the distance from the interface level because the larger the number of organizational steps between the level of analysis and the interface, the larger the number of possible configurations of substrates to produce the same outcome at the interface. Indeed, investigations at low organizational levels, such as the neuronal level, reported a higher interindividual variability compared with the behavioral level (Marder & Prinz, 2002; Marder & Taylor, 2011; Prinz et al., 2004). According to the interface principle, simplicity and predictability do not reside at the microscopic scale, as hypothesized by reductionism, but manifest at the system boundaries where the interface lies (Branchi, 2022b, 2024).

9 | IMPLEMENTING THE *CONTEXT THEORY OF CONSTRAINED SYSTEMS* IN NEUROSCIENCE AND MENTAL HEALTH

The *Context theory of constrained systems* is a hypothesis-generating framework that offers formal tools for exploring the complexity of brain functioning and the relationship between the brain and behavior. For instance, it predicts that achieving a complex phenomenon such as a behavioral response or mental state is, in most cases, accomplished using biological substrates that vary across individuals. As mentioned above, such heterogeneity increases with the growing distance between the organizational level of the biological substrate and that of the phenomenon of interest. This is mainly because of the occurrence of multiple realizability at each step between the two levels. Consequently, it is extremely rare that a single or group of genes or other biological substrates directly explain a behavioral response. In addition, the theoretical framework predicts that context is prominent in driving behavior and mental states. Since the elements that compose a complex system (e.g., biological substrates) are postulated to possess a permissive causal power while context holds an instructive causal power, the former can only influence the likelihood of a specific system outcome to occur, while the latter can actively steer it. Finally, behavior and mental states are posited to be major organizers of brain functioning, limiting the relevance of the information encoded in the biological substrates, including DNA. Therefore, brain organization is expected to differ across distinct behavioral profiles, even if the elements comprising the central nervous system are the same. These predictions are already substantiated by numerous studies mentioned above, and further investigations can be carried out to provide additional confirmation.

The theory here proposed not only provides a novel perspective for a further understanding of the determinants of brain and behavior and their interplay, but also represent the conceptual background for developing and validating innovative therapeutic strategies in the mental health field based on the brain-behavior-context system. These strategies consider behavior and mental states not as a passive outcome of a "diseased" brain but as active players capable to control and orchestrate brain functioning. Therapeutic strategies acting at the behavioral level thus represent powerful tools to regulate and reorganize the central nervous system, promoting wellbeing. In addition, as context is the major driver of behavior, therapies based on environmental interventions or promoting changes in subjective appraisal, such as psychotherapy,

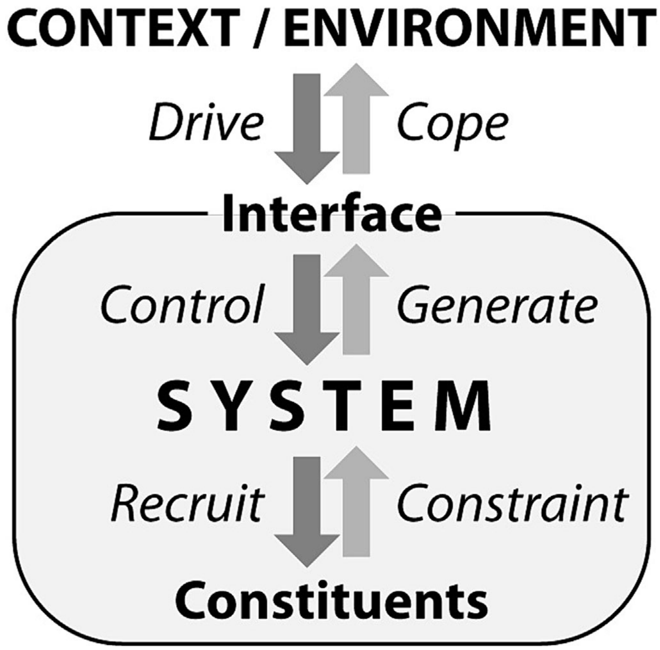

FIGURE 6 Generalizability of the *Context theory of constrained systems*. When exploring complex features of a system, the interplay among the different players involved in system functioning – the constituents, the system, its interface and the context – is generalizable. The context drives the interface because the latter is generated to cope with the contextual factors. Moreover, the interface controls the system in order to be effectively generated. In turn, the system recruits its constituents to produce the interface evoked by the context. Finally, the constituents constrain system functioning by limiting the repertoire of effective responses the system can generate to cope with the context.

modify behavior and, in turn, reorganize neural activity. For instance, interventions as green care or social farming are increasingly proven effective and psychotherapy is always an election approach in the treatment of brain disorders (Borgi et al., 2019; Vera, 2020). In addition, psychotherapy has been demonstrated to adjust the biological substrates not only in mental disorders (Dichter et al., 2010; Fu et al., 2008; Mason et al., 2017), but also in diseases affecting the entire body such as cancer (Antoni et al., 2006; Borgi et al., 2020; Chida et al., 2008; Spiegel, 2002).

Despite its relevance, the patient's context is still often overlooked in the neuroscience and mental health fields, dramatically reducing the reliability, explanatory potential and impact of studies aimed at understanding psychopathology and devising novel treatments. With some important exception (Trivedi et al., 2006), clinical trials in psychiatry rarely consider detailed information about the context, potentially missing to identify events and processes of clinical significance and of benefit to patients

(Schumann et al., 2014). A drug by context interaction thus should be considered to refine and improve the efficacy of therapeutic strategies (Carhart-Harris et al., 2018; Chiarotti et al., 2017; Ford & Young, 2022; Price et al., 2022).

10 | BEYOND NEUROSCIENCE: FROM ARTIFICIAL NEURAL NETWORKS TO URBAN SCIENCE

Since the *Context theory of constrained systems* concerns basic features of complex systems, it applies not only to the interplay between brain and behavior but can be generalized to disciplines beyond neuroscience and psychiatry (Figure 6). Indeed, the interplay among the constituents, the system, its interface and the context is anticipated to be shared by systems across multiple scales and research fields. For instance, machine learning and artificial neural networks can be framed within the *Context theory of constrained systems*. Indeed, these align with the four key points entailed by the *kitchen* metaphor: (1) the context, e.g., the training set, shapes the neural network functioning through downward causation; (2) as learning is not deterministic, multiple strategies can be implemented at the network level to achieve the same goal (i.e., multiple realizability); (3) both the training set (i.e., the environment) and the neural network structure (e.g., convolutional neural networks, capsnets, or transformers; (Abdel-Jaber et al., 2022) are key in determining the output of the network, however their role is antithetical: while the first drives the learning process, the second constrains its implementation; (4) the objective function of the neural network (e.g., the reliability of the predictions) is the cornerstone, controlling and orchestrating the entire learning process. Therefore, how machine learning and artificial neural networks work represents a potential metaphor of brain functioning and may be helpful for the theoretical and experimental progress in neuroscience (Richards et al., 2019). As a further example, the new and rapidly developing discipline of Urban science (van der Wal et al., 2021) can be framed within the same theoretical perspective: context (e.g., urbanization) drives the social organization while the social features (e.g., average income) impose constraints on the ways societies organize. A compelling and pioneering example comes from Jared Diamond's, 1997 book by *Guns, Germs, and Steel* (Diamond, 1997). It elucidates how contextual conditions across multiple scales, from a worldwide perspective to Polynesian islands, give rise to different human social structures and cultural factors, such as innovation capability and aggressiveness toward other populations.

11 | CONCLUSION

The central nervous system and its relationship with mental wellbeing and psychiatric disorders are complex phenomena that, despite the huge technological progress in the field, are still far from being understood. This can be ascribed, at least in part, to the mainstream theoretical approaches in neuroscience, based on reductionist, deterministic and mechanistic views, which struggle with the comprehension of the complexity of the brain. Here a theoretical framework, the *Context theory of constrained systems* – positing the contextual factors as drivers and the constituents as constraints of a complex system – is proposed to effectively investigate brain functioning and of its interplay with behavior. This view, illustrated with the *Kitchen* metaphor, has relevant implications at both scientific and clinical levels.

It is worth noting that the *Context theory of constrained systems* joins together several relevant theories and views in the biological and medical fields. As mentioned above, these include *Multiple realizability* (Fodor, 1974; Putnam, 1967), arguing that the same behavioral response can impinge on distinct genetic, molecular and neural substrates, *Downward causation* (Campbell, 1974; Sperry, 1980), positing that constraints of function imposed at high scales organize and define the processes occurring at lower scales, and the *Interface principle* (Branchi, 2022b), which identifies the system interface (i.e., behavior) as a privileged level of control of system (i.e., the brain) functioning. In addition, the general principle of the *Context theory of constrained systems* overlaps with Darwin's theory of natural selection and its implicit assumption of downward causation: as in the Darwinian theory, where the context selects individuals capable to cope with its challenges who, in turn, are limited by their own capabilities in doing so (Darwin, 1859), in the theoretical framework proposed here, the context selects behavioral responses capable to cope with contextual challenges which, in turn, are limited by the availability of biological elements that serve them. Furthermore, the relevance of context as key determinant of brain functioning and behavior can be broadened within an evolutionary perspective: the information carried by genes has been coded during evolution by the interaction with the context/environment (Levy, 2019). Thus, even the genetic contribution to shape the individual is indirectly determined by the context, further pointing out the primacy of the latter in shaping the individual and its functions. It is important to note that other authors have underlined the relevance of the context in biology, neuroscience and philosophy of mind (Juarrero, 2023; Oyama, 2000). For instance, it has been proposed that contextual factors are critical to elucidate the neural bases of cognitive functions (Rigotti et al., 2010) or to identify function–structure mapping within the human brain (Burnston, 2016; Viola, 2021).

In conclusion, the upward (i.e., reductionist) and downward theoretical approaches are complementary, and both are warranted to advance the neuroscience and mental health fields. Their effectiveness depends on the quality of the phenomenon to be investigated and, in particular, on its degree of complexity (Weaver, 1948). In the case of complex phenomena, such as brain functioning, their exploration is most effective if it starts from the analysis of the context and the system interface, employing a top-down approach (Branchi, 2022b). Finally, the theoretical framework proposed here and illustrated by the *Kitchen* metaphor aims at offering an innovative view to explore complex processes and, hopefully, will participate in reaping the benefits of the current huge technological advances to progress our understanding of the brain and to foster innovative strategies to achieve mental wellbeing.

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CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

No new data are described.

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