A taxonomy of neuroscientific strategies based on interaction orders

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Abstract

In recent decades, neuroscience has advanced with increasingly sophisticated strategies for recording and analyzing brain activity, enabling detailed investigations into the roles of functional units, such as individual neurons, brain regions, and their interactions. Recently, new strategies for the investigation of cognitive functions regard the study of higher-order interactions—that is, the interactions involving more than two brain regions or neurons. While methods focusing on individual units and their interactions at various levels offer valuable and often complementary insights, each approach comes with its own set of limitations. In this context, a conceptual map to categorize and locate diverse strategies could be crucial to orient researchers and guide future research directions. To this end, we define the spectrum of orders of interaction, namely a framework that categorizes the interactions among neurons or brain regions based on the number of elements involved in these interactions. We use a simulation of a toy model and a few case studies to demonstrate the utility and the challenges of the exploration of the spectrum. We conclude by proposing future research directions aimed at enhancing our understanding of brain function and cognition through a more nuanced methodological framework.

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by proposing future research directions aimed at enhancing our understanding of brain function and cognition through a more nuanced methodological framework.

1. Introduction

In recent decades, neuroscience has been characterized by an increasing ability to intervene in or record the activity of the brain across various levels of organization, utilizing a growing range of techniques and methodologies (1,2). These developments fostered investigations into the roles of neurons and brain regions, as well as the interactions between them, in relation to various cognitive and pathological conditions. New computational methods have been developed to study these interactions, extending the range of tools available to neuroscientists to an unprecedented degree (3–5).

Within this evolving landscape, certain techniques concentrate on studying individual *functional units*, such as genes (6–8), neurons (9–11), or brain regions (12,13). These techniques aim to elucidate the roles of individual functional units in cognitive functions or pathological conditions, in line with the principles of localism and modularism, which imply that specific cognitive functions or dysfunctions can be associated with neural activity in specific brain areas (14,15).

Other methods move instead the focus from the functional units to the study of their *interactions*, which are examined through various approaches, such as utilizing computational simulations or analyzing interdependencies between different brain recordings *(5)*. Within this research line, functional connectivity (FC) has become a standard method to represent brain activity as a network in which *nodes* correspond to functional units, e.g. genes, neurons or brain regions, and *edges* to statistical interdependencies between the recorded activity. This approach has unveiled new insights into brain function across a wide range of pathological and cognitive studies (16–19).

Recent research suggests that a more nuanced description of brain activity can be achieved by considering higher-order interactions, i.e. interactions taking place between more than two functional units simultaneously (20,21). This idea traces back to Hebb’s theory of cell assemblies (22), sustaining that despite structural connections being by definition pairwise, brain functions may include group mechanisms involving multiple functional units at once. The study of high order interactions has recently gained momentum and provided new insights in different research contexts, such as aging, neurodegenerative disorders, neonatal development, and more (23–33).

These lines of research focusing on individual functional units and different orders of interaction come with distinct and often complementary advantages and limitations. Techniques targeting single functional units, such as genes, neurons, or brain regions typically involve direct manipulation of these variables (9,11,34). In this way, they usually offer a clear and precise understanding of how specific neural elements contribute to cognitive processes or pathologies (35). However, they may miss crucial aspects related to the brain's systemic organization and the interaction patterns among different brain

structures (5). On the other hand, techniques that concentrate on pairwise interactions, such as FC, provide insights into the system's organization of neural activity, while maintaining a relatively straightforward interpretation (36). Yet, these methods may overlook the complexity of neural networks, where multiple units interact simultaneously in ways that pairwise analyses cannot fully capture (27,37,38). Conversely, higher-order interaction methods, which examine the simultaneous involvement of multiple functional units, have the potential to uncover more complex and integrative aspects of brain function (20,29,39), but this often comes at the cost of less interpretable results and absence of clear mechanistic explanations (21).

Combining the explanatory power of different strategies, whether focusing on individual functional units or on different orders of interaction, may be essential for advancing our understanding of the brain. To this end, a conceptual map to categorize and locate these different approaches is central and could orient researchers and guide future research directions, facilitating interdisciplinarity and the integration across different methodologies. Here we illustrate a new dimension on which different research strategies can be categorized and neuroscientific research can grow: the spectrum of order of interactions. In this conceptual map, strategies are categorized based on the order of interaction they study, facilitating the exploration and integration of approaches focused on different interaction orders, towards a more complete understanding of the brain.

The plan of the article is the following: In the first part of the paper, we define the spectrum of interaction orders, and illustrate how it can serve as a conceptual map to guide the exploration of different research practices. Then, we present its application in the study of higher-order interactions, bringing different examples to highlight the relevance of spectrum exploration (26,27,40). In the third section, we discuss opportunities and challenges arising from exploring the spectrum, highlighting that information-theoretic approaches often fall short in providing mechanistic explanations (21,41), and propose future research directions.

2. A spectrum of research strategies

Neuroscience employs a diverse array of research strategies, each tailored to specific methods and focused on different aspects of the brain and its connection to cognition. Naturally, these strategies come with distinct advantages and limitations. In this section, we present the *spectrum of orders of interaction*, which serves as a conceptual framework for categorizing different research approaches. Before delving into a more detailed explanation of the spectrum of orders of interaction, we provide examples of various investigative strategies, highlighting the order of interactions each employs, using the simulation of a horse named Artemis as a toy model to illustrate these ideas.

Artemis the horse. Let us consider a simple deterministic model of a horse, named Artemis, within an elementary environment. Artemis navigates a simulated corridor, encountering various stimuli at each time step until she successfully reaches her home. These stimuli are randomly generated in front of Artemis at each time step (Fig.1.B). By default, at each time step, the horse advances forward. When she encounters a tree, she dodges; when she comes across chocolate or bad carrots, she jumps to avoid them; when she finds a bridge to her home, with singing ducks and with an open gate, she proceeds and reaches her home. If

the bridge is either not leading to her home, lacks ducks singing, or has a closed gate, she turns back and continues the simulation.

Artemis' brain is organized into two layers of neurons: the first layer receives information from the sensory system (neurons 1, 2, 3, 4, 5, 6 in Fig 1.A), while the second layer generates responses (neurons 7, 8, 9, 10, and 11 in Fig 1.A). Brain activity supports behavior in the following ways:

- When she sees a tree (green and brown stimuli), neuron *1* and *7* fire, and consequently she dodges the tree;
- When she sees some fresh food, but not green and orange, only neuron *3* fires, followed by neuron *8* and so she avoids the food;
- When she sees green and red, but does not smell fresh food, only neuron *2* fires, followed by neuron *8,* hence she avoids the food;
- When she sees a possibly dangerous bridge, some, but not all neurons in the triplet (*4,5,6*) fire, and consequently neuron *9* fires and she turns. Note: there are five possible cases of possible dangerous bridge, reported in fig.S1.A;
- When she finds a good carrot, neurons *2* and *3* fire together consequently neuron *8* and *9* fire and since the activity of neuron *9* is suppressed by neuron *8* Artemis goes ahead;
- When she finds the bridge to his home, with ducks singing, with open gate, neurons *4,5* and *6* fire together consequently neuron *10* and *11* fire and since the activity of neuron *11* is suppressed by neuron *10* Artemis moves forward.

Now, suppose that we can only record a limited subset of neurons, specifically neurons 1 to 6, and we use that data to investigate how the brain of Artemis generates behavior. In this scenario, a possible strategy would attempt to associate the behavior of each neuron with a specific stimulus or response of Artemis, treating the rest of the system as an irrelevant background. Adopting this strategy, we could identify neuron 1 as important for dodging trees, as it consistently fires when preceded by the visual stimulus of a tree and followed by the dodging action. However, for the other neurons, we would not find a clear relationship with Artemis' behavior. For instance, when neuron 2 fires, it may lead to avoiding food half the time and eating a carrot the other half. Similarly, neurons 3, 4, 5, and 6 do not lead individually to a specific behavior and are not triggered individually by a specific stimulus. Proceeding in this way we might reveal that neurons 2 and 3 are related to eating and neurons 4, 5, and 6 are related to recognizing home. However, for neurons 2, 3, 4, 5 and 6 we could not assess clearly the functional relationship between single neural activation and behavior.

Let us now consider another approach that focuses on *pairwise interactions*, which suggests analyzing how behavior is associated with the activity of each pair of neurons. In doing so, we might observe that the joint activity of neurons 2 and 3 represents a distributed encoding of carrots, bad carrots, and chocolate, which relates to the horse's ability to avoid potentially toxic food. In fact, Artemis performs the action of avoiding food only when one of these neurons is active, but not when both are active or inactive. This behavior can only be understood by analyzing the pair of neurons together, not separately. Again, one could not understand the function of neuron 1 by relying solely on pairwise approaches, and the same applies to neurons 4, 5, and 6. A clearer picture of the function of this triplet of neurons

emerges only when considering them as a whole. In this case, one could observe that the joint state of neurons 4, 5, and 6 represents all possible cases of dangerous bridges (see fig.S1.A). Finally, one would note that the horse does not turn back only when all three neurons either fire or do not fire; in all other cases, it turns back.

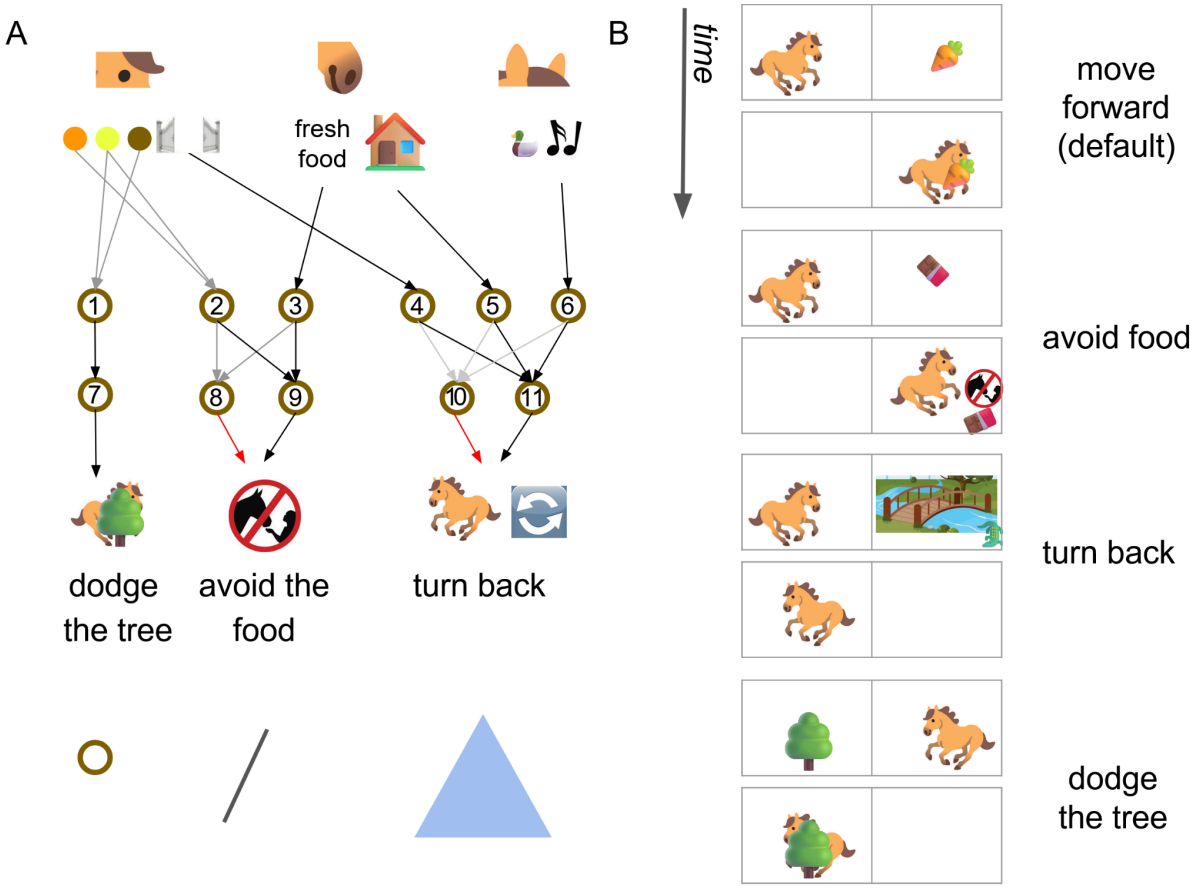

Figure 1. A toy model of the brain of Artemis the horse. (A) *The mechanisms behind Artemis are based on one XORgate and one all-or-nothing gate organized in two layers of neurons. In the scheme, black arrows correspond to synaptic weight 1, gray arrows to weight 0.5, light gray arrows to weight 0.4 and red arrows to weight -1. Circle denotes single neurons, diagonal line denotes pairwise interaction and the triangle a high-order (triplet) interaction.* ***(B)*** *Examples of sensory input and actions taken by Artemis in response to them.*

Spectrum of orders of interaction. The case of Artemis the horse is surely very simplistic and idealized. In neuroscience practices, in fact, researchers develop a variety of different experimental paradigms to inquire about the function of different neurons, and the results are gradually compared to build a coherent picture of brain properties. However, the example of Artemis can be effective in conveying the idea that a successful strategy to study the brain, given a set of experimental conditions, involves investigating brain activity across *different orders of interactions*, ranging from single functional units to groups of two, three, and higher numbers of them. By focusing on increasing numbers of neurons and their activity, one can obtain novel insights in Artemis' behavior, such as the ability of recognizing home, that can not be explained when relying solely on couples or single neurons. To provide a general

framework for contextualizing the different strategies, we introduce the notion of a spectrum of different orders of interactions, starting from order 1 to many.

Order 1. At the beginning of the spectrum, we locate methodologies that focus on single functional units. These approaches, in line with *localism* and *modularism (42,43)*, go with the idea that specific brain functions are implemented by brain structures specialized in sustaining it (11,44–47). Similarly, they are in line with Barlow's "neuron doctrine", which posits that understanding the brain can be achieved by single nerve cell recordings (11). In this part of the spectrum, we locate all approaches that decode the information that neurons, neuron population or brian regions related to a certain cognitive function in an univariate fashion, i.e. considering variables of brain activity individually (48,49). Historically, a notable finding of these strategies, at the neuronal level, is the identification of neurons that fire in response to specific stimuli in the cat's striate cortex (34). Always at the neuronal level, a more recent discovery is the identification of the 'Jennifer Aniston neuron,' a neuron that selectively activates in response to images of this particular actress while remaining unresponsive to images of other individuals or objects (9). Similarly, at the level of brian regions, for instance, BOLD signals recorded with fMRI in human orbitofrontal cortex were notably associated with specific aspects of reward and punishment (12). At the genetic level, many studies focusing on single genes unveiled notable insights about their role in shaping neural activity and behavior (6,7,35,50). A typical result of this kind of analysis would look like: *in condition A the functional units R is presenting a significantly higher/lower activation with respect to condition B*.

Order 2. Moving up along the spectrum, we encounter approaches which focus on pairwise interactions. When it is not possible to gather data about interactions and connections directly, these approaches often make use of statistical measures, such as correlations between two time series, to estimate interactions from neural recording. Typically, interactions between pairs of functional units are analyzed and compared across various cognitive or pathological conditions to determine the role of these interactions in relation to specific pathologies or cognitive functions. For instance, using fMRI, Furman and colleagues (51) studied how the correlation between brain activity recorded in the striatum and other cortical regions, varies across health and severe depression. Other findings come from the study of pairwise interactions at the neuronal levels, for instance it has been shown that learning induces changes in the interactions between neurons that are stable after learning (52). A result of a pairwise analysis on the line of the ones mentioned above would look like: *the interaction between regions R1 and R2 in condition A is stronger/weaker compared to condition B*.

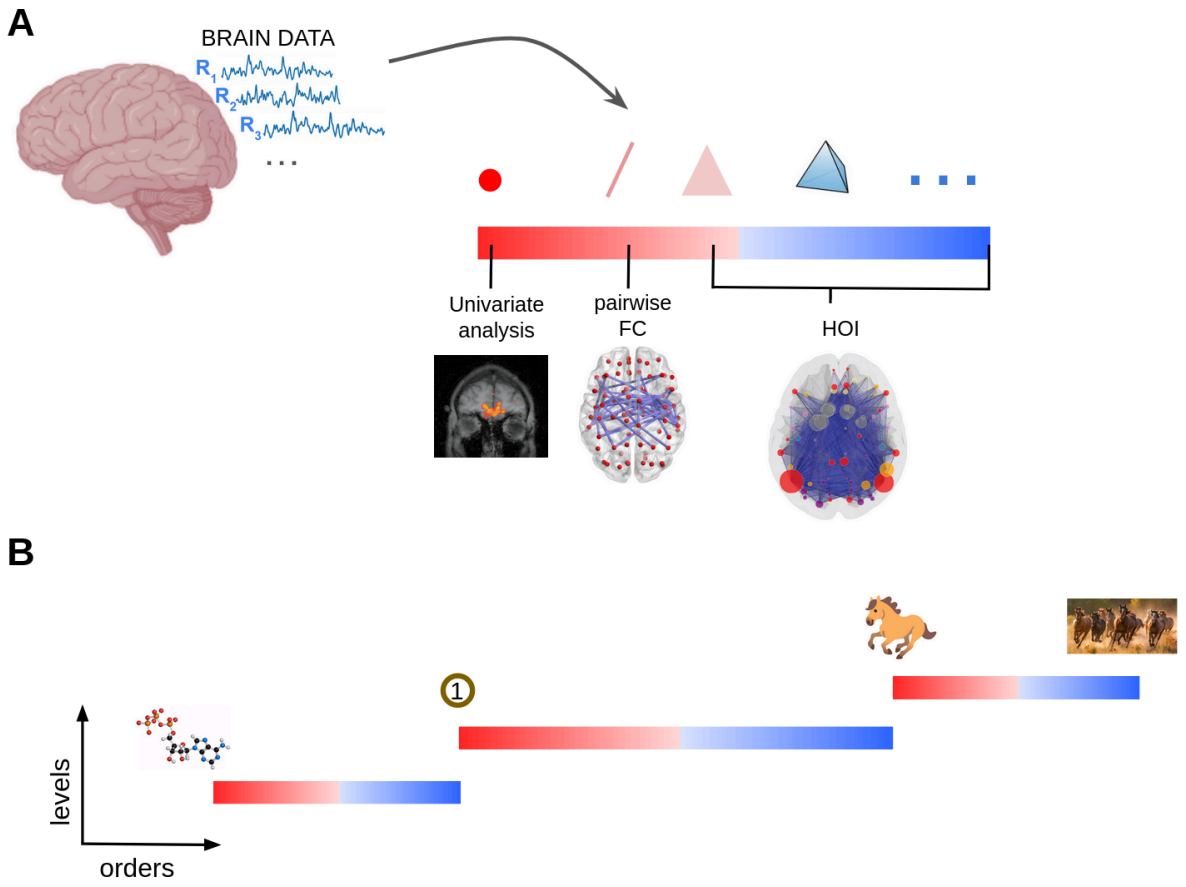

Figure 2. Spectrum of order of interactions. *Each point of the spectrum corresponds to a set of strategies investigating a specific interaction order. Methodologies are ordered following a continuum from red to blue, going from order 1 to N (the number of elements under investigation). In A), three examples of studies focusing on first, second, and higher-order analyses are presented. The univariate analysis example is from O'Doherty et al. (12), who found an association between activation in the orbitofrontal cortex and the presence of a reward during a cognitive task. The second-order analysis example is from Hong et al. (53), who reported a decrease in functional connectivity in adolescents with internet addiction. The higher-order interaction example, specifically orders three and four, is from Santos et al. (54), who investigated information patterns among groups of three or four brain regions. In B) the spectrum is depicted in relationship with the example of Artemis. A spectrum of interaction orders can be identified from single neurons (order one) to the whole brain. Similarly the spectrum can be applied to other levels, for example from 1 molecule to the whole set of molecules composing a neuron or from one horse to a collective of many horses.*

Third, fourth, and higher orders. Moving to higher order of interactions, existing approaches involve the characterization of wider multiplets and networks of interest, focusing on groups of more than 2 brain regions, neurons or genes (23–30,55). Although this area is still developing, several studies have explored interactions of order three and higher, both at the level of brain regions (26–28,56,57) and at the neuronal level (31–33,58,59). For instance in (56), the role of different triangular motifs between brain regions was evaluated and studied with respect to the

whole-brain network dynamics. Similarly, in (57), the authors focused on the effect of order three interactions in shaping the dynamics of neuronal populations observed in electrophysiological recordings. At the neuronal level, it has been highlighted the role of higher-order interactions for the emergence of synchronization (31,32) or information transmission (58). Notable contributions on this line include recent studies, which have focused on the investigation of interactions at several orders beyond pairwise, using fMRI and EEG data (26,27,60). A result of a higher-order analysis on the line of the one mentioned above would look like: *the interaction between regions R1, R2, and R3 in condition A is stronger/weaker compared to condition B*. We will have a more detailed account about this line of research in the next section.

Entire neural system under study. At the far end of the spectrum, approaches explore cognitive and pathological phenomena by examining the topological and informational properties of the entire neural system under analysis. These approaches often draw from complexity sciences (61) and focus on collective phenomena such as neuronal cascade-like events (62,63) or network-level properties (64); (65). This end of the spectrum also includes methods based on multivariate pattern analysis, which aim to measure the information conveyed by a group of brain regions to predict behavioral variables of interest (48,66). These techniques provide insights into how complex interactions across multiple regions contribute to cognitive functions and pathological states. Often they are based on pairwise representation, but focusing on the topological property of the map of interactions and not on the role of single pairwise or higher-order interactions. For instance, a notable result of this kind of analysis is the presence of well-known topological properties both at the whole brain level (64,67) and at the level of neurons (68–70). A result of a higher-order analysis on the line of the one mentioned above would look like: *brain recording presents the topological property X during condition A, but not during condition B.*

We posit that the **exploration** of the full spectrum of methodological approaches, i.e. investigating interactions at various orders, is essential for developing a comprehensive understanding of the phenomena under study. In effect, different orders of interaction can reveal distinct aspects of brain properties and functions. For instance, in the example of Artemis the horse, understanding how the brain enables the decision to avoid certain foods requires examining pairwise interactions rather than triplets or individual neurons. Conversely, recognizing a bridge, which involves a more complex decision, can only be effectively studied by investigating third-order interactions, while simple dodging actions can be analyzed already at the first order. Geometrically, these different interaction orders can be represented as a point (first order), a line segment (pairwise interactions), and the surface of a triangle (third-order interactions), as illustrated in Fig. 1A. In the Artemis' example, interactions at orders higher than three may not yield additional insights. However, one could easily modify the neural mechanisms inside the horse's brain to add interactions at order higher than 3, using similar mechanisms to the ones underpinning order *1*, *2* and *3*.

Another illustrative example of the importance of exploring different orders of interactions for understanding a system comes from computer science. Consider a laptop: traditionally, multiple organizational levels can be identified, ranging from the electric gates —that

constitute the hardware— to the software functions and programs executed by the user. At each level, exploring different orders of interactions is crucial. For instance, at the software level, if we are interested in understanding the function of the keyboard, investigating each key individually would allow us to understand how simple characters are produced. However, by examining only single keys and ignoring the interaction effects of pressing combinations of two, three, or more keys, we overlook functions such as copy-paste and typing uppercase letters. Similarly, at the hardware level, neglecting the interactions among pairs or groups of electric gates would cause us to miss essential mechanisms, which are fundamental to the operation of processors. For example, logic gates in which one unit activates only when an odd number of connected units activate could be accounted for only using a higher-order description (71). See Supplementary for a more detailed explanation.

Notably, the spectrum of orders of interactions, as a conceptual framework, can be applied to any situation in which (i) a *whole* and its *component parts* can be identified, (ii) it is meaningful to study different degrees of *interactions* between those parts (iii) in principle the whole is reducible to its components parts and their interaction. That said, it is worth noting that what counts as whole and component parts may be defined differently depending on the methodological context, and therefore may comprise different types of functional units in different types of analyses. What is whole and what are parts is decided depending on the question and the level at which a system is studied.

While our simulation specifically focuses on the activities of neurons, functional units can encompass a wide range of variables, such as genes, neurons, and brain regions (3,5). At each of these levels, the whole, its parts, and the interactions between them are defined uniquely. Levels and orders can thus be conceptualized as two orthogonal dimensions: an order of interaction can be explored across multiple levels, and within a single level, different orders can be investigated using a single dataset or multiple dataset Fig.2B. For example, at the level of brain regions, one can examine interactions between pairs of regions (second-order interactions), triplets of regions (third-order interactions), or even higher-order combinations, and these interactions may emerge from a single experimental setup or across different experimental contexts. Similarly, interactions among groups of genes, neurons, or neuronal populations can be studied at different orders (31,54,55). In fact, current computational methods allow for the analysis of different interactions across various orders by applying different statistical techniques to the same type of data. In summary, various techniques are available to study multiple orders of interactions across different levels of analysis, and each order can be examined through different techniques in the same or different set of data collected at different levels.

For instance, one could study the whole brain using fMRI data, in this case, the whole is the brain, while the component parts are modules of brain regions. In this example, the interactions under investigation are often statistical interdependencies between the BOLD recordings. There are techniques based on information theory that allow to explore multiple orders of interactions analyzing the same fMRI data. However, it also holds that at the same level of analysis, each order of interactions can be studied through different computational tools and eventually different types of data.

The conceptual framework of the spectrum of interaction orders can serve as a philosophical tool to guide and shape future research in this methodological landscape. It also can

facilitate the exploration and integration of results obtained across different interaction orders and experimental modalities. However, data and results obtained through various methods, techniques, and experimental designs can be challenging to generalize, leading to difficulties in constructing coherent interpretations of neurocognitive properties and functions (72). In the following sections, we will delve deeper into these ideas, focusing on the study of higher-order interactions (20).

3. Applying the spectrum to the study of higher-order interactions

In the previous section, we used a toy model (Artemis the horse) to illustrate the notion of a spectrum of interaction orders. Building on that simulation, in this section we demonstrate how the conceptual framework of the spectrum applies to a collection of recent approaches based on information and graph theory that have found application in various neuroscience domains. Unlike traditional network methods limited to pairwise interactions, these techniques address higher-order interactions involving more than two units of a system (20). The following section introduces key concepts behind these methods using the above principles as a unifying framework, and explains how they can uncover complex interaction patterns observed in neural systems.

General background. A long-standing tradition in computational neuroscience literature focuses on characterizing and quantifying higher-order interactions (HOIs) from neural recordings, and investigating their role in shaping brain function. Modeling and measuring these higher-order/group effects have been the ultimate goal of much research over the past few decades (59,73–76).

Information theory **(IT)** provides a principled framework to characterize higher-order interactions among neural units, particularly through multivariate generalizations of Shannon's entropy and mutual information (77). By analyzing the statistical properties of groups and individual neural variables, the Partial Information Decomposition (PID) framework (78) extends traditional information-theoretic tools to identify two qualitatively different ways in which a group of functional units can hold information (40) :

- ***Redundancy*** — refers to information held simultaneously by several variables, and thus accessible from any of the units within a group. In neural dynamics, redundancy provides robustness, as information is preserved even if individual functional units fail. For example, adding a neuron *X* with the same function as neuron *1* in Artemis' brain would create redundancy between neuron *1* and *X*. This ensures that the behavior of dodging a tree would remain intact in case one of these neurons is lost.
- ***Synergy*** — occurs when a group of variables together provides information that cannot be obtained from any subset in isolation. In neural dynamics, synergy highlights the cooperative processing of information by all neural units. For instance, in Artemis' example, synergy is seen in the combined activity of neurons 2 and 3 or among neurons 4, 5, and 6. The activity of these neurons, when considered together, offers a more comprehensive understanding of the horse's actions with respect to when the neurons are considered individually.

Studying these informational properties is particularly important for understanding the collective operations of neural populations, and the presence of synergy and redundancy can offer new insights into their interactions (78–81).

In neuroscience, higher-order information patterns can be studied in two main contexts. Directed information theoretic metrics quantify the information that a group of neural variables (sources) holds about an external behavioral variable (target). For instance, in the horse example, examining the information that neurons 2 and 3 convey about the horse's behavior could reveal strong synergy, indicating a significant gain of information when considering both neurons together. Conversely, in contexts like resting state activity, undirected metrics evaluate whether brain signals are dominated by synergy or redundancy, independently of any external target (40,82). In both these contexts, graph theory and its extensions come into play to represent and study the structure of such higher-order interactions. These can be represented in a hypergraph, i.e. a mathematical object that consists of a set of nodes and a set of edges and hyperedges (edges connecting more than two nodes). In this representation, nodes represent functional units, as brain regions or neurons, while hyper-edges connecting groups of nodes illustrate the presence of synergy or redundancy between their activity.

Overall, these lines of research can be seen as a natural extension of the FC framework, with the aim of describing and including interactions between more than 2 functional units of the neural system under exam. The spectrum of interactions as described above serves as a philosophical framework in which to locate these methodologies that investigate different orders, fig. 2.A.

Topological data analysis (TDA), within the field of topology, provides another set of powerful tools to understand higher-order interactions (83–85). These methods are grounded in the mathematical study of the properties of spaces that are preserved under continuous transformations. In the context of neuroscience, such methods allow for the characterization of the brain's structure and function in ways that traditional pairwise methods cannot. By focusing on the shape of data, topological metrics can capture the intricate, often high-dimensional relationships between neural elements.

One of the key tools in TDA, persistent homology (86,87) has been successfully applied to analyze collective dynamics of neuronal populations, uncovering robust topological features that correlate with different cognitive states or behavioral tasks (88–90). Moreover, topological approaches have been used to investigate the structural organization of the brain. By applying TDA to neuroimaging data, researchers have identified topological invariants that distinguish between healthy and diseased states, such as in the case of Alzheimer's disease or schizophrenia (91–93). By mapping neural activity onto topological spaces, researchers can identify critical points where the system undergoes significant changes, offering insights into the underlying neural mechanisms.

The philosophical framework of the spectrum of interaction orders is particularly well-suited to encompass topological methods. Unlike traditional network analysis, which often focuses on pairwise connections, topology inherently captures the higher-order relationships among groups of neural elements. Furthermore, the unifying principles of topology provide a

common language for describing these interactions, facilitating the comparison and integration of findings across different studies and experimental modalities.

Evidence of the importance of exploration of the spectrum. The broad availability of neural multivariate data and the computational methods provided by information theory (IT) and topology (TDA) allow for the exploration of a wide range of interaction orders. Typically, this line of work involves systematically measuring the interactions among groups of variables of different size present in the brain data of interest, such as gene expression data, fMRI recordings, or EEG data. We call these groups of variables multiplets, following the nomenclature for duplets, triplets, quadruplets, and so on. This entails exploring a broad portion of the spectrum of interaction orders, usually order 2 and above. In the following section, we present two examples of findings that support the exploration of the spectrum of interaction orders in neuroscience.

Herzog et al (27), show how the performance of the classification between healthy controls and patients diagnosed with behavioral variant of frontotemporal dementia (bvFTD) or Alzheimer's disease (AD) depends on the order of interaction considered. For each order *n* from 2 to 20, the authors used IT to examine the statistical interactions among multiplets of *n* variables in fMRI and EEG recordings from both patients and control subjects. Subsequently, for each order and recording modality, these interactions were used as features to classify between controls and patients. The authors observed that the classifier's performance varied with the order of interactions studied and, in particular, that pairwise interactions could never reach a classification performance as high as the one obtained with higher-order ones. Moreover, the order that allows the optimal classification between health and disease is different for the different pathologies and for recording modality. This suggests that, as in the example of the horse, different orders might be the relevant ones for different pathologies and neural phenomena of interest.

A similar approach has been used by Gatica et al in (26,37), in which the differences across age have been analyzed in terms of redundancy and synergy at different orders of interactions. In this context, Gatica et al found that redundancy increases with the order of interactions and at all orders was higher in the older part of the population. The synergy, instead, only for some specific orders was significantly higher in the younger part of the population.

Another example comes from the work of Petri et al. (92), where the authors used persistent homology to analyze brain functional connectivity during psilocybin administration—the main psychoactive component of magic mushrooms. Persistent homology examines data structures across various orders, measuring and comparing properties of groups of functional units at different interaction orders. Through this approach, the authors identified a significant topological shift in the brain’s functional patterns post-psilocybin. Notably, these changes were not captured as effectively by traditional pairwise methods, such as classical functional connectivity (FC). This case exemplifies how exploring the spectrum of interaction orders is necessary to provide a novel understanding of psilocybin’s effects on brain function.

These examples support the utility of exploring the spectrum of interaction orders, suggesting that this framework can be fruitfully employed in other contexts with different types of data and methodologies.

4. Opportunities and challenges of the spectrum exploration

Exploring different orders of interactions presents the challenge of integrating results and data obtained from approaches that focus on various interaction orders. This integration is essential for developing comprehensive explanations that account for analyses across different orders. For instance, are higher-order effects merely byproducts of pairwise interactions or could it be that pairwise interactions are byproducts of high-order? How does stimulating a single brain region influence information patterns at higher orders? These questions remain largely open and can be addressed through the integration of multiple methods and datasets.

Crucially, at each level of organization—e.g. genes, neurons, or brain regions—different orders can be investigated by applying the same statistical technique to the same dataset or by employing different statistical techniques on the same or different datasets. Hence, cross-order integration may involve combining various techniques and datasets. This form of integration is particularly valuable when merging diverse methodological perspectives, each offering unique explanations or descriptions. For example, in the cases presented below, strategies that focus on different orders and are grounded on distinct explanatory principles are combined and integrated toward a deeper methodological understanding. In the first example, the relationship between pairwise functional connectivity, higher-order information metrics, and transcranial ultrasound stimulation (TUS) is examined (94–96). In the second example, cross-order integration is used to explore the relationship between the mechanisms that govern interactions among different functional units and their patterns of statistical interdependencies (21).

The case of transcranial brain stimulation. Non-invasive brain neuromodulation, developed to alter neural activity in patients safely, has been advancing in the treatment of different conditions, such as depression (97–99), Alzheimer's (100,101) and epilepsy (102,103). A noteworthy stimulation method is the low-frequency focused transcranial ultrasound stimulation (TUS), which can precisely and safely reach both cortical and subcortical specific brain regions (94–96). However, this type of methodological advance produced a struggle between specialists on how to design stimulation protocols to obtain the desired change in neural trajectories. TUS enables targeted investigation of specific brain regions, thus strategies employing this technique can be classified as first-order approaches with respect to the spectrum we proposed. Examining the effects of stimulating a single region on interaction patterns among pairs or higher-order groups of regions offers a means to reconcile and integrate findings across different orders of interaction (cross-order integration).

Studies investigating pairwise interactions have shown changes in deep brain regions in macaques, lasting more than an hour after TUS (104). For instance, pairs of brain regions exhibit increased or decreased FC depending on the strength of their anatomical connection to the stimulation target (105). However, this effect is observed at the populational level, and it blurs when the analyses are performed individually on single subjects. Here the study of synergy and redundancy makes a difference in the assessment of the effects of the stimulation. Analyzing high-order interactions makes it possible in fact to move from population to individual characterization (37), identifying both networks that change independently of the target, and target-specific networks that are consistent across individuals. Individual characterization is key here, because it could enable tailoring therapies to individuals, a critical ingredient for external stimulation techniques.

Intriguingly, this study revealed that interventions at order 1 produce distinct effects on both pairwise functional connectivity, and higher-order informational properties. This finding underscores the importance of integrating various methodologies to assess and characterize these different orders of analysis effectively.

Studying the Mechanisms Underpinning Higher-Order Phenomena. While information-theoretic and topological approaches offer valuable insights into data, enhancing our ability to classify different cognitive and health conditions, they fall short in delivering clear mechanistic explanations. These approaches primarily reveal statistical interdependencies and coordination patterns, rather than causal mechanisms in the sense of Craver et al (41). Specifically, the information character of neural units or their topological properties indicates statistical relationships, but do not directly translate into causal mechanisms between them. Moreover, functional units, e.g in fMRI studies, often represent fluctuations in BOLD signals from parcels of brain volume, rather than discrete entities, “working parts”, as conceptualized by Craver et al. (41). This distinction has been the subject of various philosophical discussions (21,41,106,107). In essence, the distinction is between (i) methodologies that measure and analyze statistical interdependencies and correlation patterns, and (ii) approaches that seek to provide causal explanations for the mechanisms underlying brain dynamics and functions. The methods discussed in this paper clearly fall into the former category. Understanding the mechanisms responsible for these higher-order properties remains an unresolved challenge.

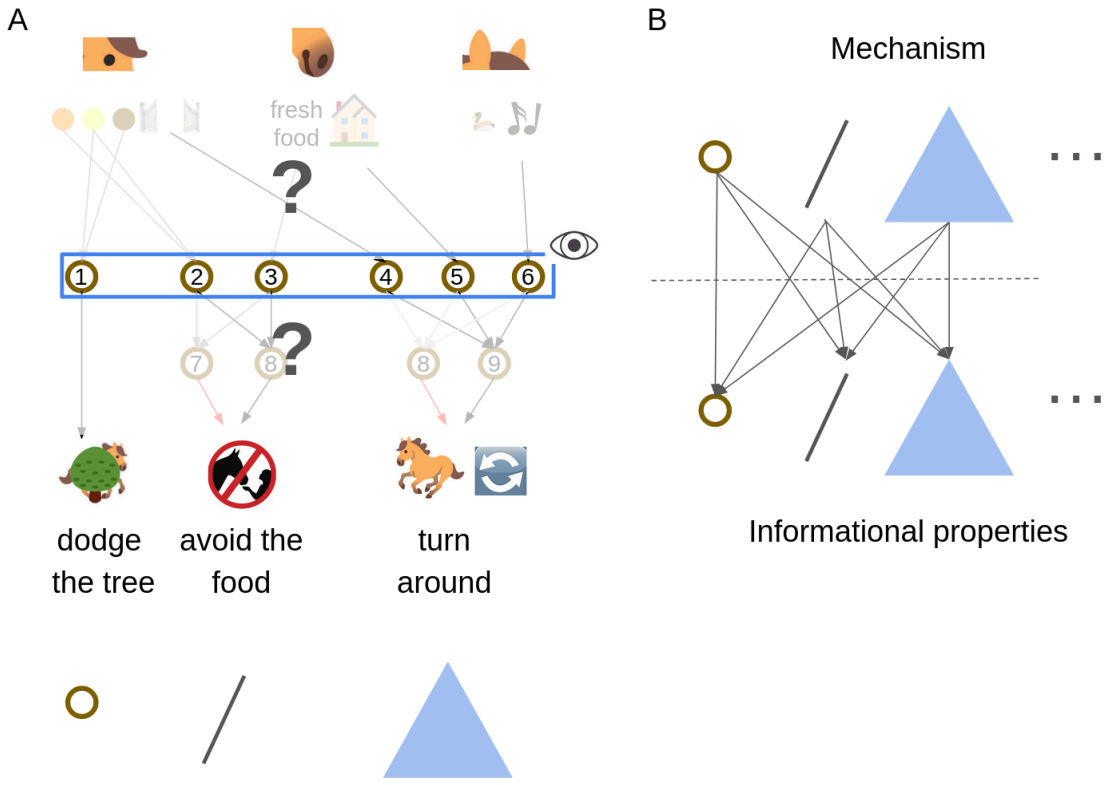

Figure 3. *The situation in which we can only measure information properties from brain signals, but we have no access to the underlying structure of mechanistic interactions* ***(A)****. A graphical representation of the daunting task of studying the relationship between informational properties and mechanisms. This implies cross-order integration since mechanistic interactions at a certain order can inflate information properties at other orders* ***(B)****.*

Understanding the mechanisms supporting synergy and redundancy and other informational or topological properties would enable us to formulate more precise hypotheses about neural phenomena, in which higher-order effects cannot be ignored. For example, in the integrative horse example, if only neurons 1 to 6 are observable, we would seek to hypothesize mechanisms sustaining their information properties (Fig. 3.A). Uncovering these neural mechanisms could significantly enhance our ability to predict, control, and treat the brain. Notably, elucidating the relationship between higher-order information and the underlying mechanisms requires integrating across different orders of interactions, since higher-order mechanisms can influence lower-order effects and vice versa (21,108), Fig. 3.B.

Few promising progress has been made in addressing this daunting task. From a theoretical perspective, using a generalized Ising model, it has been shown that statistical synergy within a group of variables indicates significant higher-order coupling (mechanism) beyond pairwise interactions (108). Additionally, in (109), the authors developed a mechanistic model bridging structural changes in connectomics with functional changes in higher-order interdependencies. Referring to the idea of the spectrum, both these studies perform cross-order integration: information patterns are analyzed across different orders of interactions in both studies and the model accounts for pairwise structural connections in (109), and for pairwise and order three interactions in (108). Other insights come from a

recent work by Gelens et al, (110), in which the authors demonstrated that long-range connections are crucial for understanding synergy during behavioral tasks. These advancements underscore the potential of integrating multiple interaction orders to bridge gaps between observed phenomena and underlying neural mechanisms.

The challenge of multiple integration. The broad applicability of the spectrum of interaction orders—to various levels and methodologies for collecting data and analyzing interactions—also relates to the challenge of integrating findings and data across different levels and methods. A clear example of this challenge was provided by Sejnowsky (1) : "*Decision-making, for example, might be studied at the level of populations of single-cell recordings in monkeys or by fMRI in humans or by lesions in rats or by molecular and optical techniques in mice. These differences mean that standardization in neuroscience must be made relative to a technique and that cross-level and cross-technique data integration cannot easily be automated.*" Indeed, the spectrum of interaction orders highlights a novel challenge: cross-order integration. This introduces a new axis along which results and data must be integrated (Fig. 4). In our representation, *techniques* refer to both the techniques used in data collection and the methodologies applied to study interactions, *levels* to the spatial scale of the investigation. For example, when analyzing the information properties of fMRI data at different orders, it is crucial to integrate these findings with the biological components of the regions under investigation (*cross-level* integration) and with results obtained from other methods, such as brain stimulation or topological data analysis of EEG recordings (*cross-technique* integration).

Preliminar progresses have been made on this line, such as associating synergy observed in brain recordings with increased synaptic activity or more complex cognitive functions (40,111,112). In the example mentioned before of Herzog et al (27), the authors also perform classification between control and patients integrating multiplets from different orders of interactions and from both recording modalities (EEG and fMRI). Doing so, they achieved the best classification, exemplifying how cross-order and cross-technique integration can enhance our ability of classifying. However, fully reconciling and integrating across different levels, techniques and orders remains an open question for future work (Fig.4). Addressing this challenge is crucial for achieving a comprehensive understanding of neural dynamics and their underlying mechanisms.

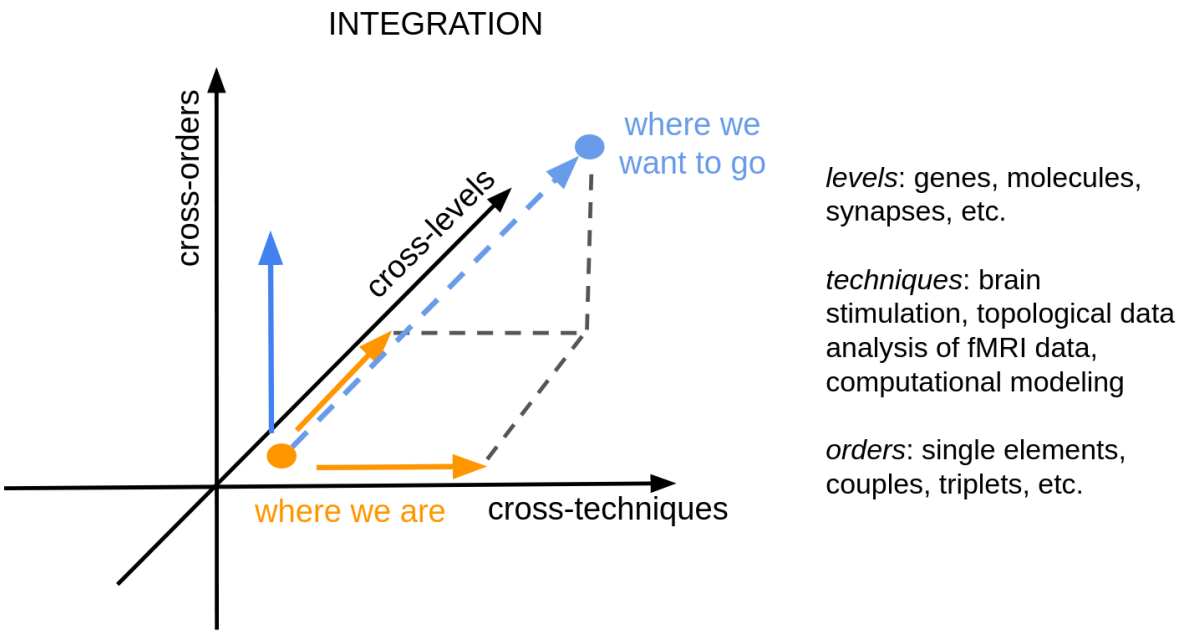

Figure 4. *A schematic representation of the integration challenges for future developments in computational neuroscience. The arrows represent the integration trajectories that are challenging future steps in the study of interactions between different units at different orders. Orange arrows represent trajectories that have already been highlighted by past studies, the blue arrow represents the challenge we present of cross-order integration. The blue dotted arrow instead points towards the challenge of integrating across different techniques, orders and levels.*

5. Discussion and conclusion

In this paper we develop a conceptual framework, based on the spectrum of interaction orders, to help scientists position and contextualize their research strategies. We introduced the possible benefits of the proposed framework through a simple toy model, and supported with several examples the idea that exploration of the spectrum represents a fundamental avenue to future advances. Finally, we discussed these ideas with respect to the growing focus of higher-order interactions, with a particular focus on information theory.

The proposal of a spectrum of interaction orders is closely related to the concept of causal composition, which posits that any group of units receiving inputs and producing outputs could, in principle, constitute a distinct mechanism within the system (113). The key distinction here is that our focus is on the methodological level of analysis. While there may not always be a direct causal mechanistic structure underlying higher-order interactions, a methodology based on the exploration of these interactions can still provide valuable insights. Integrating findings from the study of higher-order interactions, with insights coming from other methods may contribute to a more comprehensive understanding of the phenomena of interest, even in the absence of a clearly defined causal higher-order effect.

The investigation of the spectrum of interaction orders also relates to Simon's formulation of near-decomposability (114,115). This idea posits that within a system, it is possible to identify groups of strongly interacting units that exhibit relatively independent dynamics from the rest of the system on short time scales. The spectrum of interaction orders we have outlined provides a framework for exploring these interactions and characterizing such subsystems. By examining interactions at different orders, researchers can more effectively identify and analyze subsystems beyond strong form of reduction. For instance, information-theoretic metrics enable the study of a community of nodes as an integrated whole, rather than focusing only on individual nodes and their pairwise interactions, while topological methods can describe the coordinated activity of such communities across different orders of interactions (116).

In some accounts, reductionist strategies are described as those focusing solely on individual elements of the system under study, while holistic strategies consider the system as a whole (11,117,118). Following these definitions, the spectrum of orders of interaction can be viewed as a continuum of research strategies, ranging from reductionist to holistic approaches. This perspective supports the idea that both, reductionist and holistic strategies can coexist on a methodological level. It emphasizes the importance of exploring all possible approaches between these two extremes and highlights the necessity of integrating different perspectives, a challenge that must be addressed for a comprehensive understanding of the system.

In conclusion, the primary motivation behind our work is the development of the spectrum of interactions orders as a tool to guide future research toward a deeper understanding of neural functions. We propose that adopting this framework could be pivotal for advancing neuroscience, as it enhances both methodological rigor and the comprehension of complex neural phenomena. By enabling researchers to critically evaluate underlying assumptions, integrate diverse methodologies, and promote interdisciplinary collaboration, this approach has the potential to significantly contribute to the field's progress.

Data availability

The article does not have additional data.

Authors

Conflict of interest: The authors declare no competing interests.

Author contribution: M.N.: Conceptualization, writing - original draft, writing - review and editing, figures design and preparation; A.B.: Conceptualization, writing - review and editing; S.C.: Conceptualization, writing - original draft ; F.F.: Conceptualization, writing - review and editing; M.G.: Conceptualization, writing - review and editing; R.H.: Conceptualization, writing - review and editing; P.A.M.M.: Conceptualization, writing - review and editing; I.M.: Conceptualization, writing - review and editing; G.P.: Conceptualization, writing - review and editing; D.B.: Conceptualization, writing - review and editing; F.E.R.: Conceptualization, writing - review and editing; A.T.: Conceptualization, writing - review and editing; M.E.: Conceptualization, writing - review and editing.

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Supplementary

XOR. XOR (exclusive OR) gate is a digital logic gate that outputs true (1) if and only if an odd number of its inputs are true. For a two-input XOR gate, this means the output is true when one input is true and the other is false. The truth table for a two-input XOR gate is:

Input A	Input B	Output
0	0	0
0	1	1
1	0	1
1	1	0

This gate is fundamental in digital circuits, playing a crucial role in arithmetic operations, error detection and correction, and various cryptographic applications (71). In the example of Artemis, we simulated a XOR logic gate between neuron *2, 3* and the behavior of food avoidance.

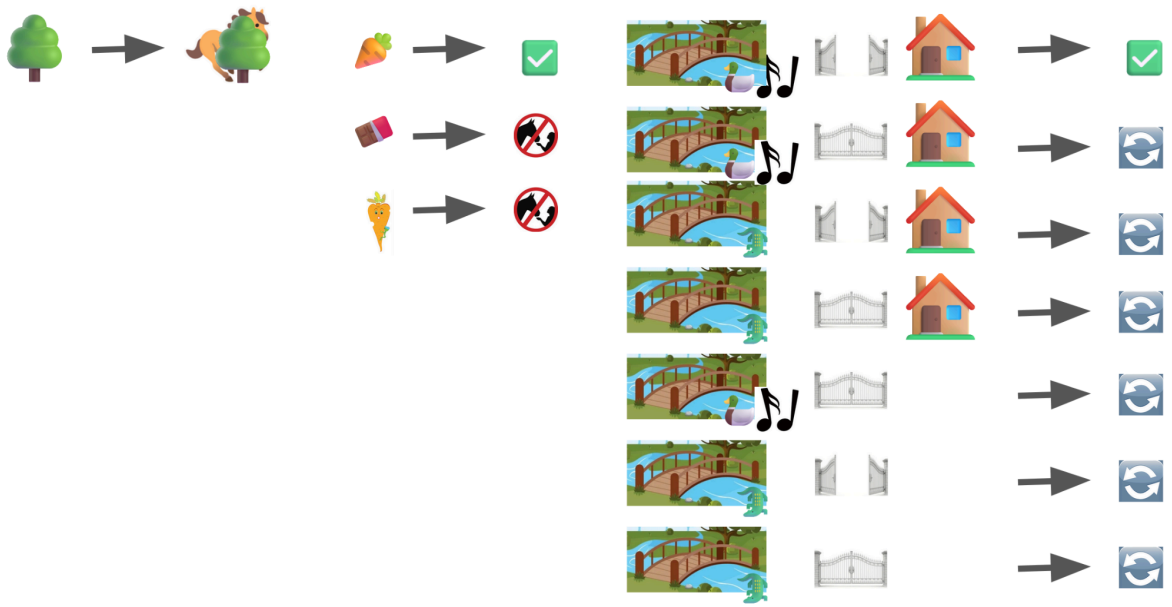

Figure S1. *All the possible combinations of input output of the integrative horse are reported here.*

Figures

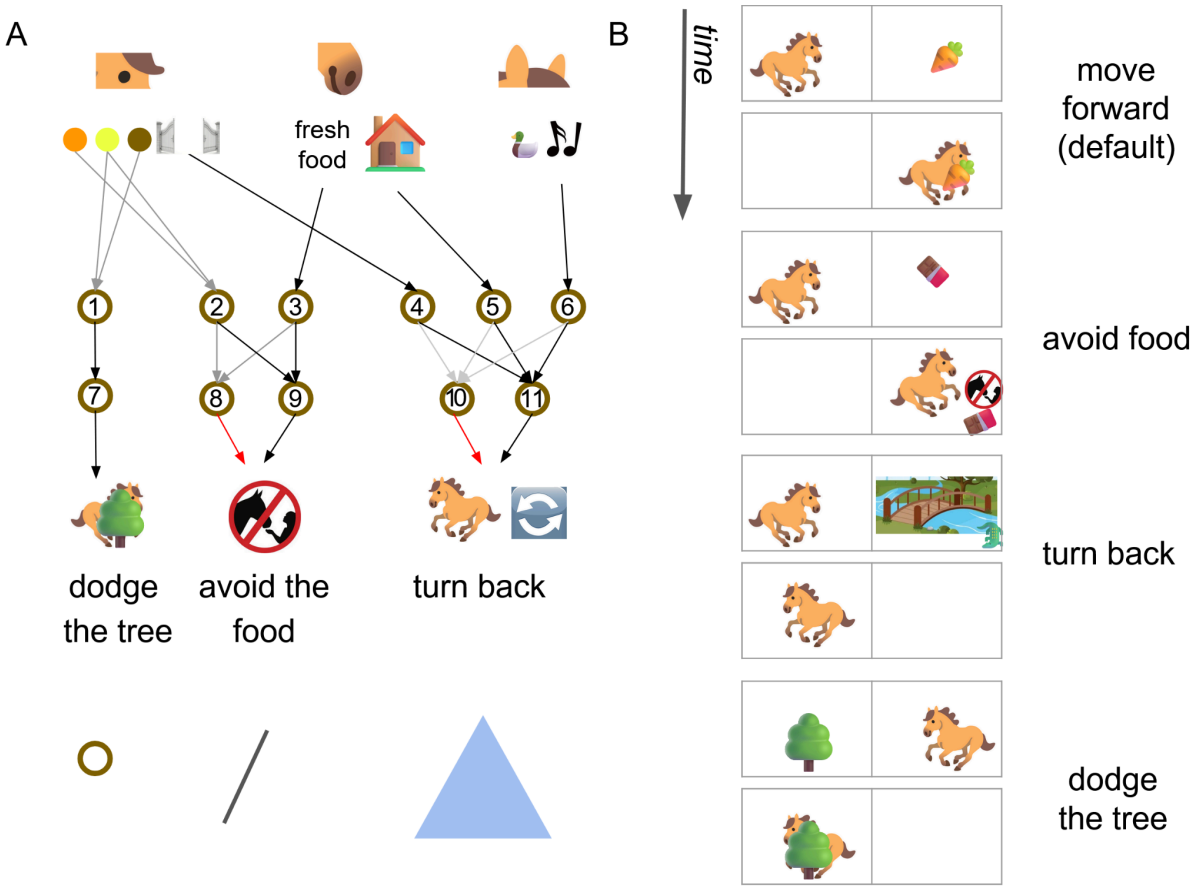

Figure 1. A toy model of the brain of Artemis the horse. (A) *The mechanisms behind Artemis are based on one XORgate and one all-or-nothing gate organized in two layers of neurons. In the scheme, black arrows correspond to synaptic weight 1, gray arrows to weight 0.5, light gray arrows to weight 0.4 and red arrows to weight -1. Circle denotes single neurons, diagonal line denotes pairwise interaction and the triangle a high-order (triplet) interaction.* ***(B)*** *Examples of sensory input and actions taken by Artemis in response to them.*

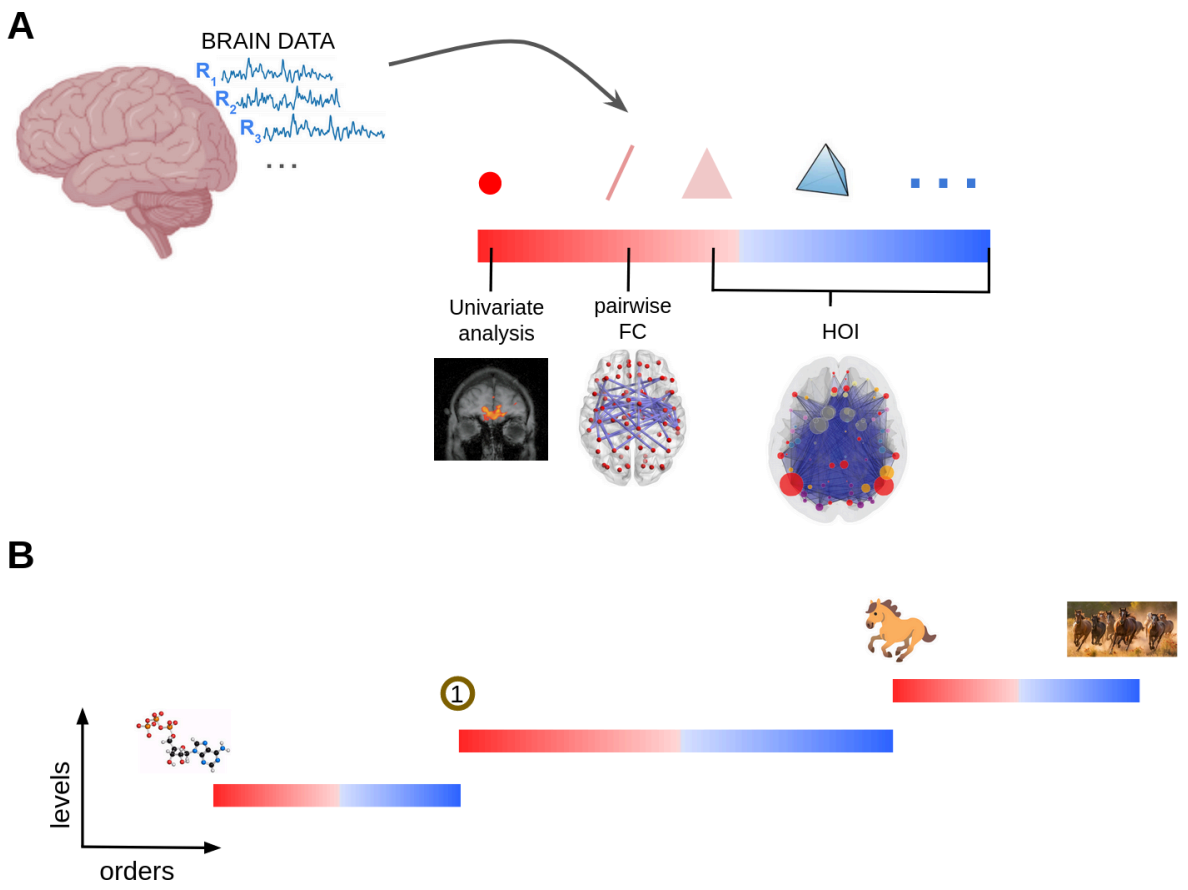

Figure 2. Spectrum of order of interactions. *Each point of the spectrum corresponds to a set of strategies investigating a specific interaction order. Methodologies are ordered following a continuum from red to blue, going from order 1 to N (the number of elements under investigation). In A), three examples of studies focusing on first, second, and higher-order analyses are presented. The univariate analysis example is from O'Doherty et al. (12), who found an association between activation in the orbitofrontal cortex and the presence of a reward during a cognitive task. The second-order analysis example is from Hong et al. (53), who reported a decrease in functional connectivity in adolescents with internet addiction. The higher-order interaction example, specifically orders three and four, is from Santos et al. (54), who investigated information patterns among groups of three or four brain regions. In B) the spectrum is depicted in relationship with the example of Artemis. A spectrum of interaction orders can be identified from single neurons (order one) to the whole brain. Similarly the spectrum can be applied to other levels, for example from 1 molecule to the whole set of molecules composing a neuron or from one horse to a collective of many horses.*

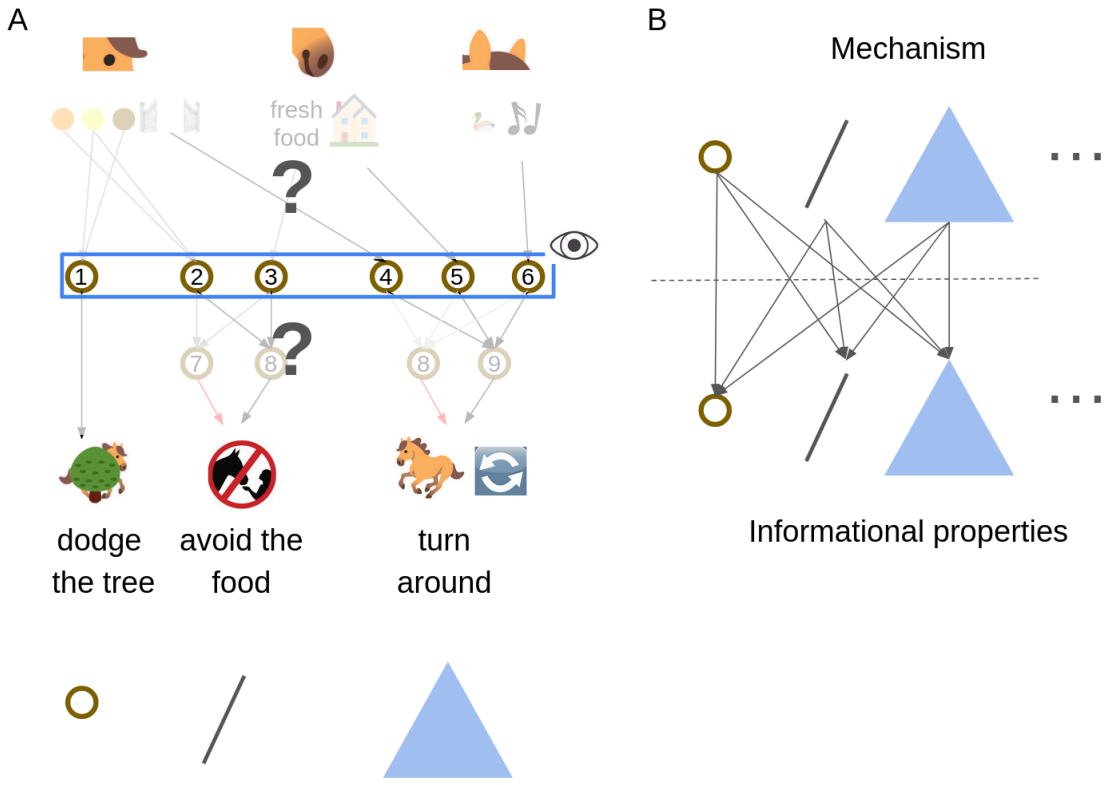

Figure 3. *The situation in which we can only measure information properties from brain signals, but we have no access to the underlying structure of mechanistic interactions* ***(A)****. A graphical representation of the daunting task of studying the relationship between informational properties and mechanisms. This implies cross-order integration since mechanistic interactions at a certain order can inflate information properties at other orders* ***(B)****.*

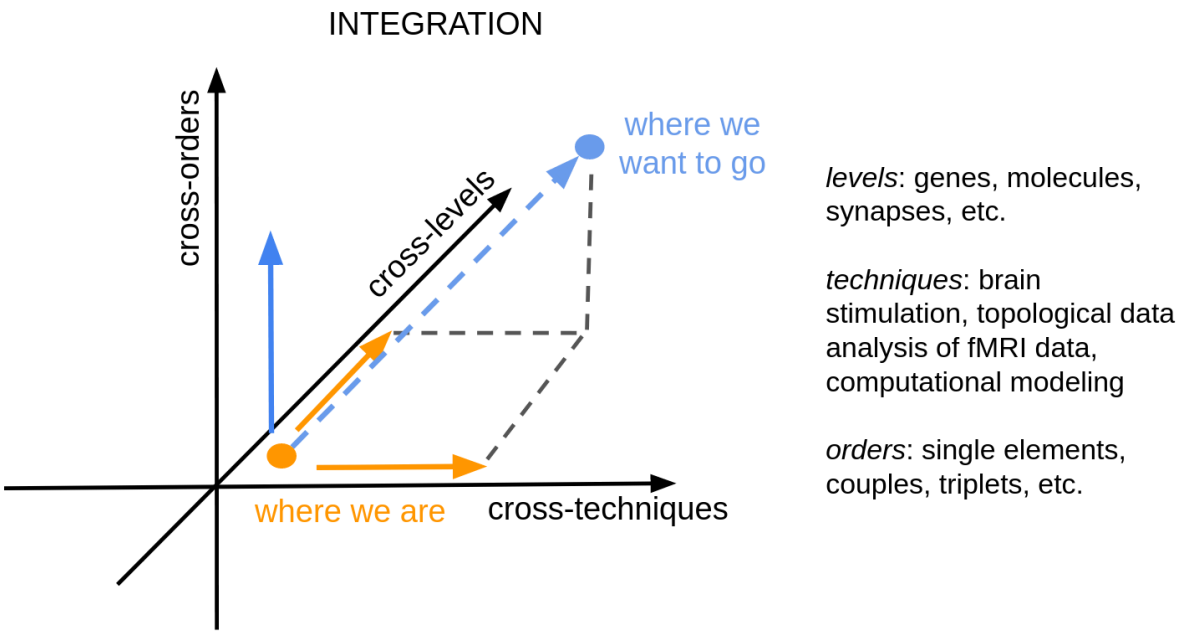

Figure 4. *A schematic representation of the integration challenges for future developments in computational neuroscience. The arrows represent the integration trajectories that are challenging future steps in the study of interactions between different units at different orders. Orange arrows represent trajectories that have already been highlighted by past studies, the blue arrow represents the challenge we present of cross-order integration. The blue dotted arrow instead points towards the challenge of integrating across different techniques, orders and levels.*

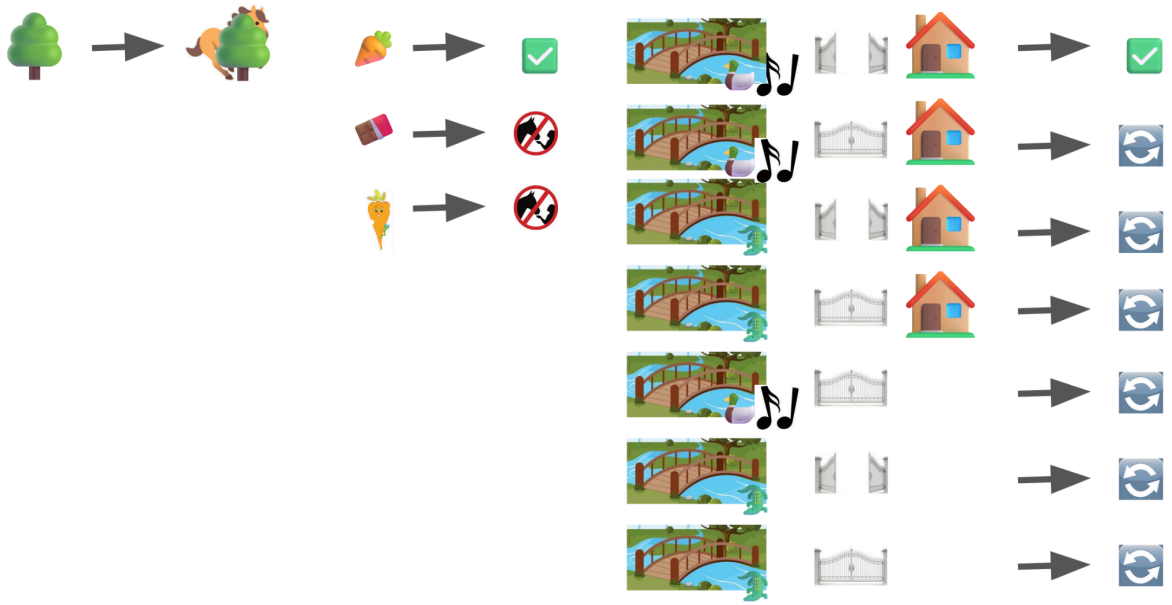

Figure S1. *All the possible combinations of input output of the integrative horse are reported here.*