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Revisiting 'brain modes' in a new computational era: approaches for the characterization of brain-behavioural associations

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The study of brain-function relationships is undergoing a conceptual and methodological transformation due to the emergence of network neuroscience and the development of multivariate methods for lesion-deficit inferences. Anticipating this process, in 1998 Godefroy and co-workers conceptualized the potential of four elementary typologies of brain-behaviour relationships named 'brain modes' (unicity, equivalence, association, summation) as building blocks able to describe the association between intact or lesioned brain regions and cognitive processes or neurological deficits. In the light of new multivariate lesion inference and network approaches, we critically revisit and update the original theoretical notion of brain modes, and provide real-life clinical examples that support their existence. To improve the characterization of elementary units of brain-behavioural relationships further, we extend such conceptualization with a fifth brain mode (mutual inhibition/masking summation). We critically assess the ability of these five brain modes to account for any type of brain-function relationship, and discuss past versus future contributions in redefining the anatomical basis of human cognition. We also address the potential of brain modes for predicting the behavioural consequences of lesions and their future role in the design of cognitive neurorehabilitation therapies.

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Introduction

One of the most important endeavours inspiring neuroscientists has been the characterization of the functional neuroanatomy of the human brain. In this mission, the advent of neuroimaging proved paramount for supporting the exploration of brain-behaviour relationships, which for the past 20 years has been providing powerful insights concerning the anatomical bases of normal and pathological cognition. As a result of this effort, the study of brain-function relationships has experienced profound transformations. Conceptually, the adoption of a connectional (hodological) systems perspective has derived a formulation of cognition subserved by hierarchically organized interactive brain networks (Bassett *et al.*, 2018). Methodologically, the development of novel computational approaches has begun the characterization of complex interaction patterns subtended by structural and functional brain networks and addressed their roles in cognition and behaviour. Additionally, this novel perspective has instigated the compilation of brain maps, integrating information on interactive properties operating dynamically across complex hierarchical neural systems.

Anticipating this transformation, pioneering work published 20 years ago in *Brain* (Godefroy *et al.*, 1998) conceptualized the regularities characterizing different classes of elementary associations between brain structures and their ability to substantiate specific human behaviours (or the lack thereof) as 'brain modes'.

Classical modes of brain-behavioural relationships

In the original paper, brain modes were defined as pre-established sets of functional interactions between cerebral regions contributing to the emergence of a neurological symptom. These entities were conceived as the means to unveil the brain's functional organization. Each mode was considered with regards to specific cognitive processes or behaviours. Anticipating the importance of a connectional perspective, this notion and the framework it generated must now be considered among the first attempts to conceptualize neurological symptoms as emerging from interactions between multiple anatomical structures organized in networks (Geschwind, 1965; Catani and Ffytche, 2005; Bartolomeo, 2011), as opposed to models emphasizing individual regional contributions.

Originally, four classes of brain modes: unicity, equivalence, association and summation, were intended to capture the full array of potential brain-behaviour relationships (Fig. 1 and Table 1). The unicity mode defined the simplest brain-function association in which a single function was linked to a single injured brain structure. The equivalence mode, the most frequently observed in clinical practice, epitomized a situation in which damage to two separate structures provoked in both cases a similar behavioural deficit. The association mode described the scenario involving two brain regions in which both had to be damaged in order to generate a neurological deficit. Finally, the summation mode characterized an interaction type in which lesions in two or more brain regions resulted in specific behavioural or clinical deficits; nonetheless, when these same structures were all simultaneously damaged, deficits proved greater than the sum of the individual lesion effects.

Illustrating 'modes' of brain-behavioural relationships with clinical examples

The originally described brain modes can be illustrated by examples of neurological and neuropsychological observations in humans, yet some exceptions and limitations apply.

The simplest brain mode, unicity, could depict the functional contributions of isolated nodes, which are hardly present in the highly and intricately connected mammalian nervous systems. Thus, this mode has been theoretically hypothesized but remains to be documented clinically. The equivalence brain mode has been documented theoretically and also clinically. Indeed, in the original paper describing brain modes, single lesions localized at two different levels along the cortico-spinal tract were characterized as equally responsible for motor weakness (Godefroy *et al.*, 1998; see also Arnoux *et al.*, 2018). Likewise, other associations compatible with this brain mode have been documented as subtending symptoms such as aphasia, memory loss, executive and attentional deficits (Alexander *et al.*, 1987; Mesulam, 1990; Kremin, 1994; Kreisler *et al.*, 2000; Godefroy *et al.*, 2009; Martinaud *et al.*, 2009; Toba *et al.*, 2018*a*, *b*). For instance, verbal paraphasias have been linked to either temporal or caudate lesions, whereas non-fluent aphasia depends on the presence of frontal or putamen lesions (Kreisler *et al.*, 2000). The association brain mode has been identified theoretically but remains to be better documented clinically, as it requires rare-to-find patients with selective lesions damaging multiple regions within the same network. This mode was originally illustrated in patients with unilateral lenticulostriate lesions (Godefroy *et al.*, 1992) showing executive function impairment only when, additionally, they suffered an associated cortical infarct. It has also been documented in cases of Balint syndrome, reduplicative paramnesia, confabulations and global aphasia (Shallice, 1988; Wolfe *et al.*, 1994;

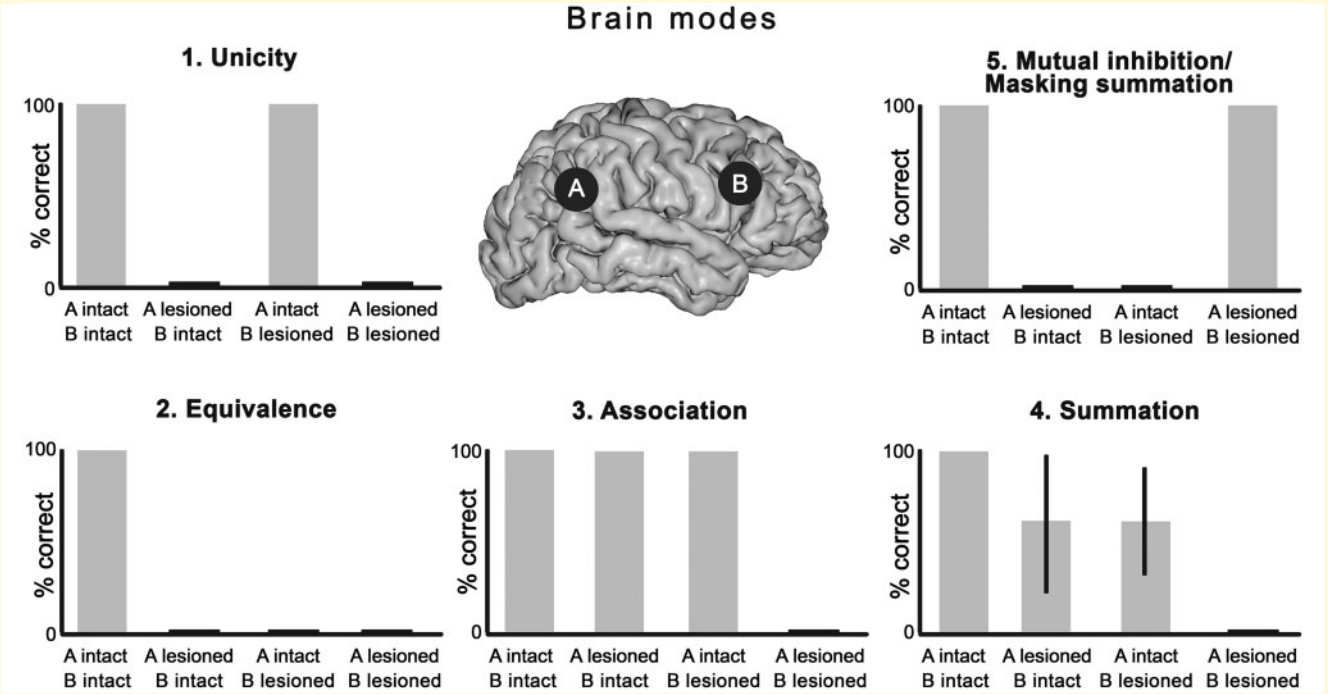

Figure 1 Brain modes. Schematic illustration of the brain modes proposed by Godefroy *et al.* (1998) and expanded here (unicity, equivalence, association, summation, mutual inhibition/masking summation) emerging from different patterns of interactions between two hypothetical cerebral nodes (A and B), here characterized with regards to their final impact on behavioural performance. Histograms display the hypothetical effect on behavioural performance, presented as the percentage of correct responses in a given task, depending on whether nodes A and B are intact or lesioned. (**1**) In the unicity mode, the behavioural deficit is linked to the lesion of a single brain region, hence 100% performance is obtained solely when node A is intact, irrespective of whether node B is intact or damaged. (**2**) In the equivalence mode, the behavioural deficit is the same if either one of two brain regions is lesioned; accordingly, 100% performance is obtained only if both nodes, A and B, remain intact. (**3**) In the association mode, the behavioural deficit is observed only when two or more brain regions are simultaneously damaged; therefore 100% of performance occurs when node A or node B are intact, but not when both are lesioned. (**4**) In the summation mode, a severe behavioural deficit is observed only when two or more brain regions are simultaneously damaged, whereas a moderate deficit is observed when only one individual region is selectively damaged; therefore, 100% performance occurs only when both nodes A and B are intact; however, when either node A or node B are lesioned there is a moderate deficit; whereas when both nodes A and B are damaged, then the deficit becomes severe. Error bars represent possible standard deviation values. (**5**) In the mutual inhibition/masking summation mode, the behavioural deficit appears when one among several regions is lesioned; whereas paradoxical behavioural recovery from a deficit occurs when both regions are jointly damaged; in this scenario, 100% correct performance occurs when both A and B nodes are intact, or paradoxically, also when both node A and node B are lesioned.

Caplan, 1995). For example, Wolfe *et al.* (1994) explored a patient with bilateral subcortical lacunae in the basal ganglia and periventricular white matter, who presented a critical level of dysexecutive syndrome after the occurrence of posterior cortical lesions. Finally, the summation mode has been documented both theoretically and clinically. For example, in language impairments, non-fluent aphasia was associated with lesions of putamen and surrounding structures while mutism was associated with large lesion of the three frontal gyri and putamen (Kreisler *et al.*, 2000; Seghier *et al.*, 2014).

Importantly, confirming the accuracy of naturally occurring lesions to illustrate specific brain modes requires detailed documentation concerning the role of lesion-spared regions, which has not always been available in neurological clinical records, as it requires the detailed whole-brain characterization of structurally and functionally sound versus impaired areas.

Limitations of classical brain mode conceptualizations

As with any pioneering work, the first conceptualization of brain modes suffered from a number of limitations, in part caused by shortcomings in the statistical and computational approaches available at the time they were first characterized. Importantly, many of these limitations can now be overcome with the use of more current methodological approaches. First, original lesion analyses were conducted only on regions of interest corresponding to anatomical structures, or to regions demarcated by brain landmarks such as sulci or gyri, as attempts to decrease region of interest size led to poor interexaminer agreement (Godefroy *et al.*, 1998). In contrast, recent lesion analyses can now be conducted at the voxel level, hence delineated at a much higher spatial resolution, allowing a more precise

Table 1 'Brain modes' (Godefroy *et al.*, 1998) and their equivalents in a multivariate approach (game-theory MSA).

Types of 'brain modes' originally reported by Godefroy *et al.* (1998) (modes 1–4) and an additional 5th brain mode (5)	Examples of 'brain modes' from lesion cases in specific regions and behavioural domains (see Godefroy *et al.*, 1998 for applications to post-stroke motor weakness)	Game-theory MSA equivalents to originally reported 'brain modes'	Application of 'brain modes' to interactive networks subtending the cognitive neuroanatomy of visuospatial attention and post-stroke hemineglect (Toba *et al.*, 2017)
1. Unicity 'brain mode' A behavioural deficit is always linked to damage of a single brain structure	Not documented (it might be an oversimplification of the motor system)	Only a single brain structure in a given coalition of players is the contributor to a function	Plausible, but not documented in this study
2. Equivalence 'brain mode' A behavioural deficit or a given level of deficit appears after damage of one, among several brain structures	Documented theoretically and clinically in aphasia, memory deficits, motor function and its deficits (Alexander *et al.*, 1987; Mesulam, 1990; Kremin, 1994; Kreisler *et al.*, 2000; Godefroy *et al.*, 2009; Martinaud *et al.*, 2009; Arnoux *et al.*, 2018; Toba *et al.*, 2018*a*, *b*)	Several brain structures are positive contributors to the function and present some degree of functional overlap	Possible, but not documented in this study
3. Association 'brain mode' A deficit is present only when two brain structures are both damaged simultaneously	Documented theoretically but remained to be better documented clinically: Balint syndrome, reduplicative paramnesia, confabulations, global aphasia, dysexecutive functions (Shallice, 1988; Godefroy *et al.*, 1992; Wolfe *et al.*, 1994; Caplan, 1995)	Several brain structures are positive contributors and present a joint functional contribution	Possible, but not documented in this study
4. Summation 'brain mode' A severe deficit appears when several structures are simultaneously damaged. *A moderate* deficit appears when only one individual region is damaged	Documented both theoretically and clinically in language (Kreisler *et al.*, 2000; Seghier *et al.*, 2014)	Several brain structures are positive contributors to the function and present redundant and synergistic interactions	Confirmed with MSA approaches: Positive contributors: BA7/IPS, BA6/FEF, BA39-40/TPJ, BA44-45/ IFG Synergistic interactions: BA7/IPS - BA39/TPJ, BA7/IPS -BA19/IOG, BA39/TPJ - BA19/IOG; BA39/TPJ - BA45/IFG, BA39/TPJ - BA40/TPJ Redundant interactions: BA44-45/IFG - BA7/IPS, BA7/IPS - BA19/IOG, BA6/FEF - BA7/IPS; BA6/FEF - BA19/IOG; BA19/IOG - BA40/TPJ
5. Mutual inhibition/masking summation 'brain mode' A second lesion produces paradoxical behavioural improvement from a deficit generated by an earlier lesion	Not discussed in the original paper by Godefroy *et al.*, (1998), but documented clinically and theoretically (Sprague, 1966; Vuilleumier *et al.*, 1996; Weddell *et al.*, 2004; Zavaglia and Hilgetag, 2016)	Several brain structures are negative contributors to a given function and they subtend synergistic interactions	Confirmed with MSA approaches: Negative contributors: BA44-45/IFG, BA19/IOG, BA6/FEF

Explanations of 'Brain modes' types are illustrated with studies presenting lesions on specific systems and the application of Toba *et al.* (2017) on visuospatial attention obtained with the multiperturbation Shapley value analysis (MSA) method (Keinan *et al.*, 2004). Specifically, the MSA approach builds on the analysis of isolated and combined regional functional contributions to a clinical deficit from a series of players (brain structures), which make part of a complex coalition (network or system). This approach allows the characterization of both positive and negative contributions of a given brain structure, which might either facilitate or hinder a selected behaviour, respectively. MSA also reveals redundant interactions (between areas with functional overlap) and synergistic interactions (between areas presenting complementary functions). Recently published studies concerning the use of MSA in post-stroke lesion data have revealed plausible evidence in favour of a causal implication of different grey and white matter structures to specific cognition domains, illustrating the potential of this approach in clinical datasets (Zavaglia *et al.*, 2015, 2019; Toba *et al.*, 2017). BA = Brodmann area; IPS = intraparietal sulcus; FEF = frontal eye field; IOG = inferior occipital gyrus; IFG = inferior frontal gyrus; TPJ = temporo-parietal junction.

characterization of brain modes. Second, the past use of structural instead of functional parcellation schemes resulted in regions with mixed functions, providing less informative evidence concerning the behavioural contributions of the analysed regions of interest. This risk can be limited by using parcellation schemes based on both structural and functional MRI (see Glasser *et al.*, 2016 for an example), further verified with perturbational approaches such as transcranial magnetic stimulation (TMS) (Toba *et al.*, 2017). Third, the original characterization of brain modes could not distinguish between grey and white matter, a limitation that is especially meaningful for the equivalence brain mode associated with white matter disconnections. Importantly, however, the advent of diffusion tensor imaging (DTI) and the adoption of hodological approaches to address brain-behavioural relationships (Boes *et al.*, 2015; Fox, 2018) has provided new insights to overcome this original limitation. Fourth, lesion

Box 1 The Sprague effect

Historical aspects and definition of the concept

Experimental animal studies in the 1960s were the first to illustrate that interactions between brain regions were unpredictable. In an effort to understand the independent and joint contributions of the visual cortex and the midbrain superior colliculus to visual behaviour, James Sprague subjected either region to lesions, and then sequentially combined the lesions. A surprising result emerged when the longstanding and seemingly intractable deficit in the detection and orienting to right-sided visual targets produced by lesion of left visual cortex was cancelled by ablation of the right superior colliculus (Sprague, 1966). This result was subsequently referred to as the Sprague effect, and was conceived by Sprague and others to be a product of manipulating mutually inhibitory bilateral interactions between brain structures (Sprague, 1966; Lomber and Payne, 1996; Hilgetag *et al.*, 1999; Lomber *et al.*, 2002; Rushmore *et al.*, 2006; Valero-Cabré *et al.*, 2019).

Confirmatory aspects

This experimental work was used in part to formulate mechanistic understanding of visuospatial neglect (Kinsbourne, 1974, 1977, 1987, 1993). Later findings in neurologically intact human participants (Hilgetag *et al.*, 2001) and in human clinical cases (Vuilleumier *et al.*, 1996; Weddell, 2004) provided considerable evidence that the mechanisms underlying the Sprague effect contributed to analogous interactions in humans. Kinsbourne's ideas and the aforementioned clinical cases exerted major influences in understanding the brain-wide impact of unilateral brain damage in humans, wherein damage was presumed to reduce activity in connected brain regions in the ipsilateral hemisphere and increase activity in the contralateral hemisphere through disruption of inhibitory circuits (Murase *et al.*, 2004; Nowak *et al.*, 2009). Until now, the best evidence of the Sprague effect has been observed at the interhemispheric level.

Consequences in therapy and in the comprehension of the human functional neuroanatomy

This approach guided the later use and interpretation of non-invasive brain stimulation studies, in which focal inhibitory stimulation [including low frequency TMS, continuous theta burst TMS, or cathodal transcranial direct current stimulation (tDCS)] aims to transiently take offline focal cortical regions while recording behavioural performance (Valero-Cabré *et al.*, 2017). This approach has been successfully applied to the intact brain hemisphere in patients with unilateral brain damage (Oliveri *et al.*, 1999; Brighina *et al.*, 2003; Koch *et al.*, 2008; Sparing *et al.*, 2009; Koch *et al.*, 2012; Cazzoli *et al.*, 2012) and proved to restore neurological deficits caused by focal brain lesions, such as hemispatial neglect. All these studies demonstrate that the mutual inhibition/masking summation brain mode has already opened new avenues for therapeutic uses of non-invasive brain stimulation technologies. However, this new brain mode has also opened perspectives of improving visuospatial orienting abilities in healthy humans (Hilgetag *et al.*, 2001). Looking to the future, we should envision that reversible neuromodulation technologies [TMS, repetitive TMS or tDCS/tACS), which are currently helping to investigate the cognitive role of cortical regions embedded in brain networks, could also be used to probe or unearth existing and novel brain modes. Moreover, the use of these same technologies for the modulation of specific site or sites implementing a given brain mode may prove useful to develop novel strategies for the restitution of neurological function.

characterization approaches used in the late 1990s were unable to grade the magnitude of the neural damage, hence ignoring the crucial role of lesion volume threshold effects on neurological deficits. As such information becomes available for other anatomical grey and white matter systems, this important aspect will be better controlled (see Arnoux *et al.*, 2018 for an example of the threshold level of cortico-spinal tract injury generating significantly enduring motor deficits at 6 months). Fifth, multivariate analyses proposed in the original characterization of brain modes were based on one particular type of statistical approach, the so-called Classification and Regression Tree (CART) (Breiman *et al.*, 1984). This method was able to disentangle important factors in terms of explanatory power in a model, and provided naturally the type of logical relationships between selected regions. However, the CART approach requires large datasets and additional statistical analyses to assess the strength of brain-behavioural associations. The latter limitations can now be overcome by current multivariate methods for lesion-deficit mapping providing more appropriate and reliable analysis tools (see below).

New brain modes: the case of mutual inhibition/masking summation

At the time they were first described, brain modes represented a major conceptual advance in the field, aiming to represent any known lesion effects by their four original types. Nonetheless, multivariate CART approaches originally used for their characterization failed to identify 'paradoxical lesion cancellation' effects, initially reported in feline models (Sprague, 1966; Payne *et al.*, 1996; Hilgetag *et al.*, 2002) and later extended to human neurological patients (Kinsbourne, 1977, 1987; Vuilleumier *et al.*, 1996; Weddell, 2004; Johnson *et al.*, 2008; Jha and Brown, 2011), known as the 'Sprague Effect' (Box 1).

This phenomenon described the paradoxical improvement of performance deficits caused by a circumscribed lesion thanks to a reversible or permanent suppression of activity in a second brain area interacting with the former (for reviews see Payne and Rushmore, 2004; Valero-Cabré *et al.*, 2019). Inspired by predictions of interhemispheric rivalry in spatial attention in the feline visual system, this brain mode was also characterized in humans using causal reversible perturbation by TMS (Hilgetag *et al.*, 2001). Intending to transiently impair lateralized visual detection performance in one visual hemifield with inhibitory repetitive TMS on the contralateral intraparietal sulcus, these authors found paradoxical improvements for ipsilateral visual targets. This unexpected result revealed that a reversible focal suppression of human brain activity could produce attentional and perceptual gains. Further studies in animals reported paradoxical cancellation of lesion-induced

deficits with secondary focal lesions, direct cortical cooling or non-invasive TMS deactivations of spared cortical and subcortical attentional orienting systems (Rushmore *et al.*, 2006; reviewed in Valero-Cabré *et al.*, 2019).

We here propose to name this additional brain mode 'mutual inhibition' or alternatively 'masking summation' and add it to the palette of existing typologies.

Logic operators and circuit motifs for characterizing brain modes

Since their inception, brain modes were conceived of as elementary building blocks that, adequately combined in complex fashions, could account for any specific neurological deficits. Here we revisit brain modes from the perspectives of logic and propositional calculus as well as graph theory approaches and the concept of circuit 'motifs'. We suggest that analogies between brain modes and elementary units used especially in the graph theory framework are particularly suited for analysing and extending the existing typologies, and further exploring their implications for cognitive neuroanatomy.

From the perspective of logic, some of the brain modes can be characterized as standard forms of logical relationships between unary and binary factors, and represented with a standard truth table. For example, with respect to a brain function, 'unicity' can be associated with identity; 'equivalence' may be equated to conjunction (AND); 'association' could be associated to disjunction (OR); and 'mutual inhibition/masking summation' corresponds to the opposite of an exclusive disjunction (NOT XOR or XNOR). The 'summation' brain mode may not be fully captured by binary logical operators as its outcome depends on the graded interactions between the nodes. Of note, other authors have proposed weighted extensions of logical functions that can express partial conjunctions and disjunctions (Dujmović and Larsen, 2007) and which could be used to describe such relations in the context of the summation mode. Generally, in order to characterize the graded effects of brain modes, one might also use arithmetic (rather than logical) operations, which can be extended and turned into actual circuit models capturing the observed effects (*cf.* Zavaglia and Hilgetag, 2016).

In the graph theory framework, brain modes can be based on different 'brain motifs' (Fig. 2). These represent plausible types of interregional relationships with the ability to influence a given brain function. In this regard, the unicity mode would be the equivalent of a node (i.e. brain region) defined as the only contributor to a brain function. Damage of a unique contributor generates a level of behavioural deficit that depends on the magnitude of the impaired contribution and the extent of the lesion. Hence, the unicity mode could be well suited to describe brain-behaviour interactions in which function emerges from single nodes. The equivalence mode is observed when behavioural performance in a given task benefits from multiple contributions by different nodes, which contribute similarly to a behaviour. The association mode represents the case of joint contributions of two (or several) nodes to a given behaviour, in which a critical level of clinical deficit manifests only when both nodes are injured. The summation mode is observed when two conditions apply to a given set of nodes: (i) each node provides a specific contribution to a given behaviour; and (ii) their contributions are both redundant (overlapping) and synergistic (complementary). Last, in the masking summation mode, two nodes interacting with each other contribute to a brain function. Clinical deficits appear present only when one of the two nodes is lesioned; however, symptoms can paradoxically wear off when the two nodes are jointly damaged, by the fact that they are linked by rivalrous mutually inhibitory interactions. Taken together, the equivalence, association, summation and/masking summation modes characterize a hodological framework in which behaviours (or the lack thereof during neurological diseases) emerge from nodes organized in networks. Such interactions can be summarized in a simple two-node circuit model (Fig. 2) that formalizes arithmetically the strength of functional interactions and contributions of the nodes. Importantly, the number and complexity of brain motifs, and the elementary types of brain modes they implement, depends on the number of regions involved. As the number of nodes increases, the complexity of directed network motifs and their contribution patterns escalates (Fig. 2).

To conclude, the generalization and combination of brain-behaviour relationships by means of propositional calculus allows a partial description of the brain modes space, but does not facilitate the modelling of non-binary relationships, which grows in complexity as the number of interacting areas increases. In this context, other frameworks, such as graph theory, should be explored to better characterize these entities and further extend the variety of their typologies.

Revisiting brain modes from a multivariate analysis perspective

Multivariate modelling integrating different anatomical variables and considering the presence or absence of damage to multiple brain regions simultaneously may help to extend the analysis of brain modes (Godefroy *et al.*, 1992, 1998; Keinan *et al.*, 2004; Chen *et al.*, 2008; Chen and Herskovits, 2010; Smith *et al.*, 2013; Mah *et al.*, 2014; Zhang *et al.*, 2014; Rondina *et al.*, 2016; Yourganov *et al.*, 2016; Toba *et al.*, 2017; Xu *et al.*, 2018). These methods, which are committed to replace univariate approaches, are now widely used in the field, and may allow a better characterization of the canonical brain

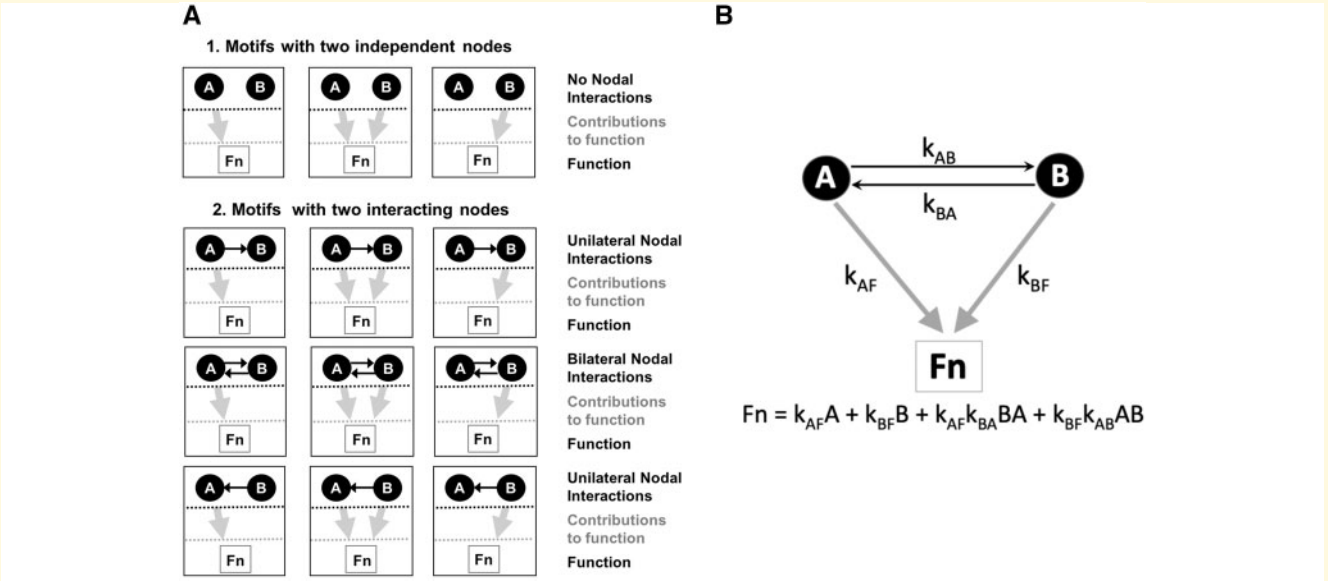

Figure 2 From brain modes to brain motifs. (**A**) Brain motifs. Graphical representations of 'brain motifs' defined as plausible connectional patterns (i.e. brain circuits or networks) established by interacting brain regions and their ability to influence a given brain function, denoted as Fn. Brain motifs can be considered as the anatomically or functionally plausible implementation of brain modes as brain circuits or networks. Here we decided to present brain motifs based on combinations of only two, either independent or potentially interacting brain regions, referred to as nodes A and B. Nonetheless, the number and connectional complexity of brain motifs, hence the number and types of brain modes that they implement, can easily scale up when considering interactions between a higher number of regions, as it is often the case in the brain. For example, three and 13 brain motifs define all possible relation types between two or three nodes, respectively. However, a full characterization of networks composed of four nodes will demand 199 motifs, and such numbers would then have to be multiplied by all possible combinations of potential contributions (i.e. three combinations for systems of two nodes: just node 'A' or node 'B' or both 'A' and 'B' contributing, seven combinations for three nodes, etc.). Thin black horizontal arrows represent interactions (unidirectional or bidirectional) between brain nodes A and B; larger grey arrows represent contributions (or influences) of nodes A and B to a given brain function, denoted Fn. (**1**) *Top row*: Three brain motifs between two independent (non-interacting) nodes in three different scenarios. *Left*: Only node A contributes to a brain function Fn; *middle*: two nodes (A and B) contribute to a brain function Fn, hence nodes could present functional overlap; *right*: only node B contributes to brain function Fn. (**2**) *Top, middle and bottom rows, from left to right*: Plausible brain motifs between two interacting nodes according to nine different scenarios. Three different general patterns can characterize interactions between nodes A and B via directed connections to influence function Fn. *Top row*: Node A projects to node B; *middle row*: nodes A and B mutually project to each other; *bottom row*: node B projects to node A. Moreover, these three patterns can be combined with three types of nodal functional outputs to influence function Fn. *Top row:* Only node A directly contributes to function Fn; *middle row*: both nodes A and B contribute to function Fn; *bottom row:* only node B contributes to function Fn. Single black arrows represent a node (A or B) interacting unidirectionally and serially with the other node, to ultimately influence brain function Fn; bidirectional black arrows represent nodes contributing in parallel to ultimately influence brain function Fn. Depending on the type of interaction, the functional contribution provided by nodes A and B could be higher (synergy) than the sum of their individual functional contributions. Joint contributions may not necessarily be the exact sum of individual contributions; indeed, this scenario would be equivalent to the absence of functional interaction between nodes A and B, hence depicted as independent nodes. Notice that for synergistic (complementary) functional contributions, nodes should interact via structural connections. Importantly, several brain motifs represented here may produce similar behavioural outcomes despite different underlying network structures. The full set of directed two-node motifs is represented for symmetry reasons. It is tempting to compare brain modes with brain motifs (particularly for those depicted above involving two brain regions) and search for common features that could substantiate the former as being the same as the latter. In the 'unicity' mode, an independent (non-interacting) node A should be the unique contributor to a brain function Fn. In the 'equivalence' mode, both nodes A and B should contribute to a brain function Fn without redundancy, for instance, by A contributing to Fn serially through B. In the 'association' mode, both nodes A and B should contribute in parallel to brain function Fn. Finally, in the 'summation' mode, both nodes should also contribute in parallel to a brain function Fn. Additionally, however, they should interact, redundantly or synergistically. In any case, the mapping between these two notions, brain modes and brain motifs, is not always straightforward and some of the brain motifs presented in this figure and the many that could be theoretically conceived with more than two nodes, cannot be unequivocally characterized in terms of a single 'brain mode', especially if one aims to take into account the number and type of functional interactions between the nodes. A possibility to reveal the rich set of functional interactions of some brain motifs consist in removing connections between nodes. In particular, this is possible in computationally implemented 'ground-truth' models, by systematically exploring the parametric space of possibilities, and 'virtually' damaging nodes and links in all possible ways to then use such evidence to infer the network structure from associated changes in brain function. However, it is more difficult to infer all these different 'motifs' directly from changes in brain function after perturbing different nodes and/or the links between them. (**B**) Algorithmic summary of brain motifs and modes. Summary of the minimal circuit interactions of two brain nodes A and B potentially contributing to a brain function Fn. The equation formalizes the strength of the interactions and functional contributions of the nodes, and appropriate settings of the path coefficients might capture all brain modes and motifs displayed in (**B**). Specifically, setting all paths except k_{AF} to zero corresponds to unicity; setting k_{AB} and k_{BA} to zero correspond to association; while leaving all coefficients non-zero can yield, with the right parameter settings, equivalence, summation or masked summation.

modes while helping to describe new typologies (see Table 1 showing applications of a multivariate method to explore brain-behaviour relationships and Box 2 for critical issues concerning formalization of lesion parameters in multivariate modelling) (Bzdok *et al.*, 2017; Price *et al.*, 2017; Xu *et al.*, 2018). Moreover, the use of brain modes as sets of elementary types of associations on brain-function relationships would constrain multivariate approaches increasing their ability to deliver reliable outcomes. However, promoting a rigorous use of multivariate methods for such endeavours requires raising awareness of some critical issues impacting on their practical implementation.

First, defining the 'hypothesis space' is an essential step for making accurate inferences and predictions of brain-behaviour relationships in the context of complex models such as those introduced by multivariate methods. Recently published attempts have used hypothesis-based approaches pre-selecting a few sets of regions, composing a coalition of contributors, which can then be tested together as part of the same model (Toba *et al.*, 2017). Nonetheless, more advanced methodological avenues use bias-free identification strategies, that can test sets of regional contributors, grouped as part of specific coalitions, without *a priori* assumptions (Zavaglia *et al.*, 2019).

Considering the large spectrum of multivariate methods, Bayesian approaches based on *a priori* defined hypotheses have been useful to narrow down the number of relevant brain sites included in multivariate models (Chen and Herskovits, 2010; Duering *et al.*, 2013, 2014; Arnoux *et al*, 2018). Nonetheless, hypothesis-free identification methods based on machine learning algorithms play a major role in formal hypothesis and model generation (Xu *et al.*, 2018). For example, in the equivalence brain mode, when multiple lesion sites cause the same impairment, machine learning tools can generate predictive multivariate models, incorporating simultaneously information from multiple voxels without the need of *a priori* hypotheses (Hope *et al.*, 2013; Smith *et al.*, 2013; Price *et al.*, 2017). Interestingly, this same approach can be used to identify key variables and generate predictive models, contributing to the identification and classification of new brain modes. Moreover, by integrating structural/functional neuroimaging, neurophysiological recordings and non-invasive brain stimulation, multivariate machine learning tools will reach full potential and drive a better understanding of functional anatomy (Price *et al.*, 2017). Nonetheless, these approaches are also costly in terms of computational time and need of independent training datasets. Moreover, machine learning algorithms operating as 'black boxes' often run into serious risks of inferring irrelevant relations due to overfitting. Last but not least, to date, even the most sophisticated multivariate machine learning lesion analysis methods are unable to disambiguate the independent effects of different lesion sites in absence of patient datasets showing such dissociations.

Second, artificial ground-truth models (Mah *et al.*, 2014) may help overcome some of the former limitations, and may become the 'gold standard' method to characterize and validate past and future brain mode typologies. Indeed, the original conceptualization of brain modes was tested via simulated populations of patients, and later confirmed in datasets from real-life stroke patients with motor disabilities. Different ground truth models able to manipulate the variability of anatomical patterns have been proposed (Inoue *et al.*, 2014; Mah *et al.*, 2014; Zhang *et al.*, 2014; Sperber and Karnath, 2017; Pustina *et al.*, 2018). In particular, computationally implemented ground-truth synthetic models have the potential to reveal complex functional interactions between brain regions and explore the parametric space of possibilities by removing, with graded levels of severity in all possible ways, 'virtual' nodes and/or connections between sets of chosen regions of interest. Such evidence can then be used to infer network structure from associated changes in brain function. Last but not least, these same methods can prove useful for lesion-deficit anatomical mapping and ultimately for clinical predictions.

Box 2 Critical issues to be considered for the formalization of lesion parameters to characterize brain-behaviour relationships with multivariate models

- Ponder carefully the risk of characterizing regions of interest as being either totally lesioned or completely spared by using fixed binarized damage thresholds.
- Employ a conservative lesion parametrization strategy, particularly when operating at the voxel level; this is a particularly sensitive issue for perilesional areas in the absence of functional MRI data informing on tissue viability.
- Implement whenever possible a transnosological approach, which compares complementary lesion datasets from distinct neurological conditions characterized by different symptoms.
- Prioritize the use of continuous over discrete or binarized variables when estimating the magnitude of behavioural performance or quantifying the severity of clinical scores.
- Consider two potential scenarios with regards to the localization of neuronal clusters (voxels) responsible for a given function (or the lack thereof):
  - (i) A cognitive process enabled during a clinical task is subserved in a large majority of studied individuals by neuronal clusters localized within the same brain region/regions.
  - (ii) The localization and magnitude of activations linked to a cognitive process enabled during a clinical task presents as highly variable across studied individuals, and is subserved by neuronal clusters localized in very different brain region/regions.

  For example, across the same cohort of individuals, neuronal clusters (brain regions) activated during the access to word meaning are more consistently located and activated in magnitude than those required to access the meaning of specific words, which may highly differ across individuals (Binder *et al.*, 2009; Lambon Ralph *et al.*, 2017).

Future directions

Two decades after its first theorization in 1998, the concept of brain modes remains a guiding framework in which to better characterize brain-behaviour associations and study their implementation in plausible structural and functional networks. Significant conceptual and methodological advances in multivariate analysis place the systems neuroscience community in an excellent position to reframe the inventory of the brain modes and critically evaluate the exhaustiveness of these relationships to define a comprehensive set of brain-behaviour associations. In particular, current brain mode typologies could be refined by comparing predictions made by computational lesion studies implementing a theoretical model (based on simulations of reliable structural and functional interactions among brain regions) with empirical results from brain lesion datasets. Moreover, as we look to the future, we can anticipate the need to apply brain modes to personalized clinical rehabilitation programmes (Nachev *et al.*, 2018). More specifically, data on brain modes hold the potential to inform computational modelling and web-based platforms able to simulate large-scale networks using biologically plausible structural and functional connectivities (Sanz Leon *et al.*, 2013). This type of environment (for example in *The Virtual Brain*; thevirtualbrain.org) allows the construction of personalized configurations of structural and functional systems, and the study of brain dynamics under the influence of focal and network perturbations or disorders, simulating, for example, epilepsy or the cognitive consequences of stroke (Falcon *et al.*, 2015). They may provide predictive tools to investigate the impact of brain structural alterations on neural dynamics (Alstott *et al.*, 2009; Aerts *et al.*, 2016), study the remapping of function-specific brain modes and contribute to the planning of better strategies for cognitive rehabilitation or neurosurgical interventions. We look forward to the realization of the potential of the brain modes approach over the next 20 years.

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Competing interests

In the past 5 years, O.G. has served on scientific advisory boards and as a speaker (Novartis, CSL-Behring, Biogen, Genzyme, Lilly, Bristol-Myers Squibb, Boehringer-Ingelheim, Covidien, Teva and Astra Zeneca), and has received funding for travel and meetings from Novartis, Lilly, Genzyme, Astrazeneca, Biogen, Teva, Pfizer, CSL-Behring, GSK, Boehringer-Ingelheim, Ipsen, Covidien and Bristol-Myers Squibb.

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