In search of morphological modules: a systematic review

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ABSTRACT

Morphological modularity arises in complex living beings due to a semi-independent inheritance, development, and function of body parts. Modularity helps us to understand the evolvability and plasticity of organismal form, and how morphological variation is structured during evolution and development. For this reason, delimiting morphological modules and establishing the factors involved in their origins is a lively field of inquiry in biology today. Although it is thought that modularity is pervasive in all living beings, actually we do not know how often modularity is present in different morphological systems. We also do not know whether some methodological approaches tend to reveal modular patterns more easily than others, or whether some factors are more related to the formation of modules or the integration of the whole phenotype. This systematic review seeks to answer these type of questions through an examination of research investigating morphological modularity from 1958 to present. More than 200 original research articles were gathered in order to reach a quantitative appraisal on what is studied, how it is studied, and how the results are explained. The results reveal an heterogeneous picture, where some taxa, systems, and approaches are over-studied, while others receive minor attention. Thus, this review points out various trends and gaps in the study of morphological modularity, offering a broad picture of current knowledge and where we can direct future research efforts.

Key words: morphological modularity, phenotypic integration, developmental modules, functional modules, EvoDevo.

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I. INTRODUCTION

Modularity is thought to be a ubiquitous property of natural complex systems that emerges at all hierarchical levels of organization (Simon, 1962; Callebaut, 2005). The organization of the phenotype into modules is the result of the interplay between genetically and epigenetically controlled developmental processes, and the functioning of morphological structures in their environment (Pigliucci & Preston, 2004; Schlosser & Wagner, 2004; Callebaut & Rasskin-Gutman, 2005). A common developmental origin, a shared allometric growth pattern, a joint performance of a function, or a shared evolutionary history, are all examples of factors that can promote the integration of body parts into morphological modules. Moreover, modularity is a fundamental concept in biology that helps us to understand the complexity of the genotype–phenotype map and the evolvability of the organismal form (von Dassow & Munro, 1999; Bolker, 2000; Müller, 2007; Pavlicev & Hansen, 2011). In recent years, many essays and narrative reviews have laid the foundations for an empirical research program on morphological modularity based on developmental, ecological, and evolutionary mechanisms (e.g. Raff & Raff, 2000; Schlosser, 2002; Pigliucci, 2003; Wagner, Pavlicev & Cheverud, 2007; Klingenberg, 2008, 2014; Kuratani, 2009; Murren, 2012; Goswami *et al.*, 2014; Rasskin-Gutman & Esteve-Altava, 2014). A common message from all these studies is that a deeper insight into the modular organization of living beings is essential to understanding the development and evolution of form. What we lack is a panoramic view of how we have approached the study of morphological modularity to date, a view that helps us to identify the basis of our current knowledge and the gaps that require further research.

This review compiles and evaluates 205 original research articles that report the presence and/or validate hypotheses of morphological modularity in animals and plants. Through a systematic quantification of the study materials, methodological approaches, and results obtained in these research articles, this review seeks to answer the following specific questions:

(1) what are the sources of our knowledge on morphological modularity and where are the gaps (if any)?

   (a) Is morphological modularity ubiquitous in all living beings?
   (b) Is morphological modularity equally pervasive in all body parts?
   (c) Are there biases in the study of morphological modularity?

(2) How do we study morphological modularity?

   (a) What biological criteria do we use to propose hypotheses of modularity?
   (b) What methods do we use to test these hypotheses?
   (c) Do the same biological factors explain modularity and integration patterns?

(3) Which are the most acknowledged morphological modules in different organisms and morphological systems?

(1) A minimal definition of morphological module and integration

The simplest definition of a morphological module is a group of body parts that are more integrated among themselves than they are to other parts outside the group (Eble, 2005). Integration arises as a direct consequence of the number and strength of interactions, regardless of how we define interaction (Eble, 2005). This minimal definition of morphological module uses the concepts of integration and interaction deliberately vaguely, with the intention of being more inclusive. Because it makes no reference to why or how integration among parts originates and varies (nor to the source of this integration), it applies to a wide range of morphological systems. In fact, by replacing 'body parts' with 'elements of a system' this definition applies even to non-biological systems (Simon, 1962). The concept of body part has also a broad sense to accommodate semi-independent structures (e.g. head, limbs) and individual elements within a larger structure (e.g. cranial bones, petals of a flower), as well as individual traits, morphometric measures, and their proxies (e.g. landmark coordinates). This minimal definition of morphological modularity has a broader range of applications than the traditional definition of morphological integration and modularity, which is related to a structure of covariation of shape and size (Terentjev, 1931; Olson & Miller, 1958), and hence it applies also to other sorts of morphological information (e.g. proportions, connections, articulations and orientations; see Rasskin-Gutman & Buscalioni, 2001; Rasskin-Gutman, 2003). I will henceforth refer to this minimal definition of a module in order to bring together as many research studies as possible, regardless of the morphological system, methodology, and factors of integration used.

(2) On factors of integration and modularity

In practice, any particular study turns the above minimal definition of morphological module into an operational definition by specifying the factors behind integration (or parcellation, i.e. the formation of modules) and the meaning of body part. This is a common, essential step in the quantitative study of modularity. One of the problems of bringing together different types of morphological studies is that the definitions of module and of integration change depending on the level of organization and the type of factor guiding the study (see Eble, 2005, for a conceptual review).

Cheverud (1996) describes four levels at which morphological integration occurs, based on the types of interactions established among body parts and the mechanisms involved: functional, developmental, genetic, and evolutionary. The actual realization of these interactions might involve various processes and mechanisms, such as the distribution of biomechanical forces among body parts, the diffusion of signalling molecules, or the inheritance of genetic

regulatory networks controlling development. According to Cheverud (1996): at an individual level, function integrates parts that perform the same or related tasks and need to coordinate during performance; development integrates parts that interact during their formation, including those controlled by the same genetic network; at a population level, genes integrate parts that are inherited together (often due to pleiotropy: a single gene affecting multiple parts); and evolution integrates parts that evolve in a coordinated manner because they are inherited or selected together. For a review of how genetic, developmental, functional, and evolutionary modules relate to each other see Klingenberg (2008). Other authors have proposed additional or complementary factors of integration. For example, Wagner & Altenberg (1996) introduced the operational concept of the variational module as correlated sets of traits that arise from a given configuration of the genotype–phenotype map (e.g. some traits covary because the same group of genes have pleiotropic effects on both of them). In addition, Chernoff & Magwene (1999) argued that the organization of parts in the body integrates those parts that share structural relationships due to geometric and/or topological interactions. In his essay on the conceptual basis of morphological modularity, Eble (2005) introduced a distinction between variational modules (*sensu* Wagner & Altenberg, 1996), which are used to study how morphological parts covary during evolution and/or ontogeny, and organizational modules, which capture the structural relations among body parts in individual organisms. This distinction is essential in order to understand that not all morphological modules need to be related to a structure of covariation of shape and size. For example, morphological modules in the human brain identified by its functional activity using functional magnetic resonance imaging (fMRI) are not necessarily linked to a pattern of covariation of shape of brain modules (but see Gómez-Robles, Hopkins & Sherwood, 2014). More recently, Mitteroecker & Bookstein (2008) introduced another distinction between factors, regardless of their origin: global factors maintain the cohesion of a morphological system (integration factors), while local factors provide internal cohesion of its modules (parcellation factors). The latter classification of factors stresses the fact that we usually do not know whether each type of factor described above is uniquely related to the formation of morphological modules or to the integration of the whole phenotype. In fact, the hierarchical nature of the phenotype suggests that the effect of a particular factor in the integration or parcellation of a body part depends on the scale at which this factor acts (Bastir, 2008).

(3) On methods to study morphological modularity

Concepts such as morphological integration and modularity are not exclusive of one school of thought, but shared (with their particular nuances) by a large community of biologists. Form is a rich concept that encompasses not only the shape and size of a morphological system but also its structure, i.e. the number and arrangement of parts (Rasskin-Gutman & Buscalioni, 2001). Acknowledging a broad definition of form helps us to value the use of different, complementary methods to quantify form and to assess patterns of modularity and integration.

There are many methods available to infer and validate modules in morphological systems, the most commonly used being morphometrics (i.e. the quantitative analysis of shape and size). Two different traditions coexist within morphometrics: linear and geometric morphometrics. Linear morphometrics captures shape as linear distances between landmark points, whereas geometric morphometrics captures shape as geometric configurations of landmark points. Other differences between these two approaches are mainly related to, for example, how they deal with size corrections, relative position of landmarks, or the use of different statistical methods (for further details see Zelditch *et al.*, 2004, pp. 1–20). During the last 20 years, the use of geometric morphometrics to quantify shape variation in evolution and development has increased considerably, as a consequence, in part, of the advent of more-sophisticated software for image digitization and statistical analysis (e.g. Adams, Rohlf & Slice, 2013). It is beyond the aim of this review to argue for or against any particular method of inquiry; rather the aim is to show the pattern of use in current research. However, it is worth mentioning that within the community of researchers using morphometrics there is still an open debate on whether some methods are better suited than others to identify (or validate) morphological modules (see e.g. Magwene, 2009; Mitteroecker & Bookstein, 2009; Garcia, de Oliveira & Marroig, 2015; Adams, 2016).

Network analysis also has been introduced to study the structure of complex morphological systems such as the human brain (Sporns, 2011). Network analysis is common in neurosciences to identify modules, for example, using community detection algorithms (Fortunato, 2010), because the very structure of the brain, as a web of neurons, is readily modelled as a network (Sporns, 2011). A network is a formal abstraction of a system, in which nodes represent the parts of the system and links represent their relations (e.g. structural, developmental, functional). The analysis of network models helps to identify groups of parts that have more connections (i.e. interactions, relations) among themselves than they do to other parts outside the group (see Section I.1). Network analysis also has been applied more recently to study the morphological modularity of the human head: the nodes of the network represent the bones and muscles of the head, connected through their physical interactions (e.g. Esteve-Altava *et al.*, 2013, 2015*bb*; Esteve-Altava & Rasskin-Gutman, 2015).

This novel use of network models in anatomy should not be confused with the use of 'graph modelling', a method that uses graphs to represent phenotypic correlations of morphometric traits or landmarks in statistical analyses (e.g. Magwene, 2001, 2008; Zelditch, Wood & Swiderski, 2009). Notably, graph modelling of morphometric traits correlations has been used together with network analysis to study the modules of the mandible in mammals (Perez *et al.*, 2009) and of the insect wing (Suzuki, 2013).

II. METHODS

(1) Gathering of original research articles

The studies reviewed comprise only peer-reviewed original research articles that explicitly assess morphological modularity (i.e. testing or reporting a modularity pattern). The articles included herein are not limited to those testing explicitly an hypothesis of modularity. Articles reporting a modularity-related pattern (e.g. whole-system integration, hierarchical integration of parts, or modular organization) using descriptive or exploratory approaches are also included. This decision was made to take into account exploratory studies and to offer a broader picture of research into morphological modularity in different disciplines. Thus, the general criterion was to include papers that: (*i*) have at least one of certain key words (see below) in their titles and (*ii*) test or describe a modularity/integration pattern. The number of articles explicitly testing any hypothesis, and the amount and type of hypotheses tested are among the variables analysed herein.

I searched in *Google Scholar* for articles including in their title at least one of the following key words: functional integration, genetic integration, modular evolution, modularity, morphological integration, mosaic evolution, ontogenetic integration, phenotypic integration, pleiades, evolvable, and evolvability. The year of publication of the landmark book *Morphological Integration* by Olson & Miller (1958) was used to set the beginning of the search. So as not to exceed the limit of 1000 entries in *Google Scholar*, I performed a separate search for each year between 1958 and 2015 inclusive.

Google Scholar has high coverage (100% for medical systematic reviews) despite its low precision (i.e. many entries retrieved are irrelevant) (Gehanno, Rollin & Darmoni, 2013). This means that *Google Scholar* can be used in systematic reviews with a low likelihood of missing relevant references. Unfortunately, a search method using the title alone means that some relevant research articles might be excluded from the sample if their titles do not include the above key words. The aim of the search then would be to retrieve a sufficient number of studies that represent the general picture of research into morphological modularity.

The search retrieved more than 5500 results of which 610 matched the selection criteria. I updated and searched the full text of each relevant article using EndNote X7 through several institutional journal subscriptions (Universitat Jaume I, Universitat de València, Universitat Autònoma de Barcelona, Royal Veterinary College, and Howard University), public repositories, personal webpages, and personal requests. A total of 205 articles remained (see online Appendix S1) after excluding duplicate entries, non-original research articles (e.g. books, book chapters, essays, and other reviews), and articles that did not assess morphological modularity. Two articles were included twice in the data set (Magwene, 2001; Klingenberg, 2009), because they comprised two independent studies, each requiring separate evaluation.

(2) Evaluation of original research articles

For each entry in the data set I collected the following information (details of how information was coded are also given):

(1) *Year of publication.*

(2) *Field of the journal of publication*: the field was assigned according to the journal description in the following categories: anatomy, anthropology, general biology, botany, cell biology, development, ecology, EvoDevo, evolutionary ecology (EvoEco), evolution, generalist, genetics, medicine, neurosciences, palaeobiology, physics, physiology, and zoology.

(3) *Taxa*: the genus, family, order, class, phylum, and kingdom of the specimens used in the study were coded as different variables. For simplicity, only the lowest rank that included all the specimens of a study was coded. For example, a study comparing primates and rodents was coded as class Mammalia, while order, family, and genus were coded as not applicable (NA).

(4) *System of study*: a descriptive label of the system used in the study, for example, cranium, body parts (i.e. comparison among different structures such as limbs and head), flower, or brain. More-inclusive labels were used when various components are studied; for example, a study analysing the cranial vault together with the brain or with attached muscles would be coded as 'head'.

(5) *Type of material*: this was coded as being fossil or living, while the label 'both' was used when the sample included extinct and extant species.

(6) *Type of tissue*: for vertebrates, 'hard tissue' was used for studies analysing skeletal and cartilaginous samples; 'soft tissue' was used for tissues other than bones and cartilage (e.g. brain, muscles, organs); and 'both' was used when the study included hard and soft tissues.

(7) *Scale of the study*: this variable codes for the temporal scale of the analysis. 'Microevolutionary' refers to studies at the population level or including only one species; 'macroevolutionary' refers to studies comparing different species or higher taxa; 'ontogenetic' refers to studies comparing different developmental stages; 'case study' refers to studies analysing only one specimen or a very small sample ($N < 5$). Studies combining these scales were labelled accordingly (e.g. MicroEvo/MacroEvo).

(8) *Number of hypotheses tested*: the integer number of hypotheses the article tested explicitly. NA is used for articles that did not test any hypothesis, but instead performed a descriptive or exploratory analysis and reported a modularity or integration result.

(9) *Specific hypotheses tested* (if any): a description of the modules tested. The coding term 'integration' is used when the hypothesis explicitly tested is the absence of modules, that is, integration of the entire system studied.

(10) *Criteria used to define these hypotheses*: a list of different variables was evaluated and coded independently. The list captures the most-frequent criteria identified in the data set: anatomy, development, function, genetics, growth,
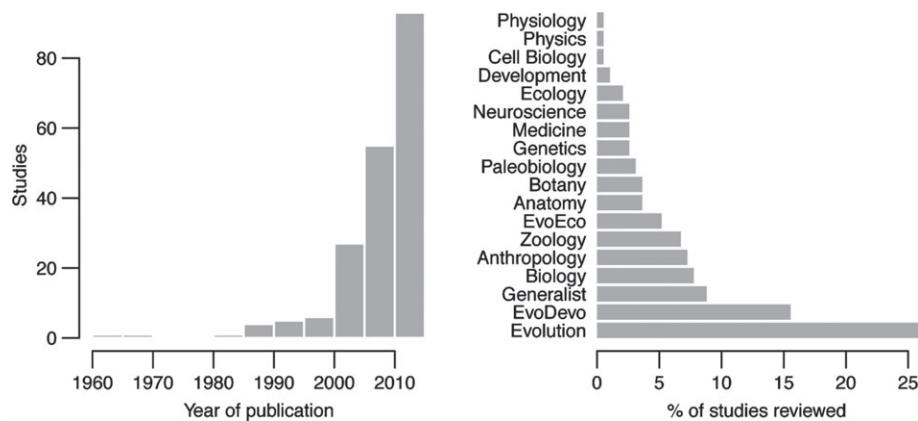
Fig. 1. Number of publications on morphological modularity between 1959 and 2015 and the research fields of the journals in which the reviewed literature appeared.

origin, shape, size, timing, and others. For each variable, '1' indicates that authors used this criterion explicitly or implicitly as a source to derive their hypotheses. Each variable is coded separately as '1' if more than one hypothesis is tested or one hypothesis was based on several of the criteria listed. For example, anatomy and function would be coded as '1' in a study that tests a hypothesis of modularity based on the anatomical structure of the system and its function.

(11) *Methods used to identify or validate morphological modules*: a list of different variables was evaluated independently. The list captures the most-frequent criteria identified in the data set: biomechanical performance, geometric morphometrics, heterochrony (i.e. by association of developmental timing), linear metrics, network analysis, qualitative description, quantitative trait loci, and others. Each variable is coded separately as '1' if authors used this family of methods. For example, a study that uses geometric morphometrics and quantitative trait loci would be coded as '1' in both variables.

(12) *Results obtained*: three variables capturing separately whether the study validates a proposed hypothesis (1) or not (0), whether the study reports whole-system integration (1) (i.e. absence of modularity) or not (0), and the specific result of the study regarding the presence of modules (if any).

(13) *Factors argued for these results*: a list of different variables was evaluated independently. The list captures the most-frequent factors identified in the data set: developmental, environmental, functional, genetic, growth, phylogeny, topological, or none. Each variable is coded separately as '1' if authors used this type of factor to support their results. For example, a study that reports that development is the sole cause of a modular organization has '1' in the variable 'development'. Multiple factors are possible.

Finally, the Pearson's product moment correlation coefficient was used to evaluate the possible association between every pair of variables using the function *cor.test* in

R (R Core Team, 2015). The evaluation of the research articles is shown in Appendix S1. The protocol scripted for its analysis in *R* is provided in Appendix S2. An extended account of the results of the data set analysis is shown in Appendix S3.

III. RESULTS AND DISCUSSION

Empirical research on morphological modularity has grown exponentially in the last 25 years. Almost half of the reviewed articles were published in journals with a strong focus on evolutionary biology, with the remainder published either in specialist or generalist journals (Fig. 1). This publishing pattern highlights a rising interest in morphological modularity in the biological community, and in particular, of its impact on understanding of development and evolution. Below, I summarize the main results, additional details are provided as extended results in Appendix S3. In general, there is no strong and/or significant evidence of correlation between any pair of criteria, methods, factors, and results reported (see Section 8 of Appendix S3).

(1) Preferences that bias our knowledge on morphological modularity

The presence of modular organization in all organisms has a solid conceptual and empirical foundation, however, most of our knowledge about morphological modularity comes from the study of mammals (61% of articles reviewed), with a strong focus on primates and rodents (Fig. 2A). At the genus level, *Homo* (19%) and *Mus* (11%) are the most-studied taxa. This bias might be explained by our particular interest in our own species and the use of mice as a model species, rather than by their suitability to answer questions about morphological modularity. The number of articles devoted to plants (11%) and to arthropods (10%) is surprisingly low. The study of phenotypic integration in plants has a long tradition (e.g. Berg, 1960; Pigliucci *et al.*, 1991; Diggle, 2014),
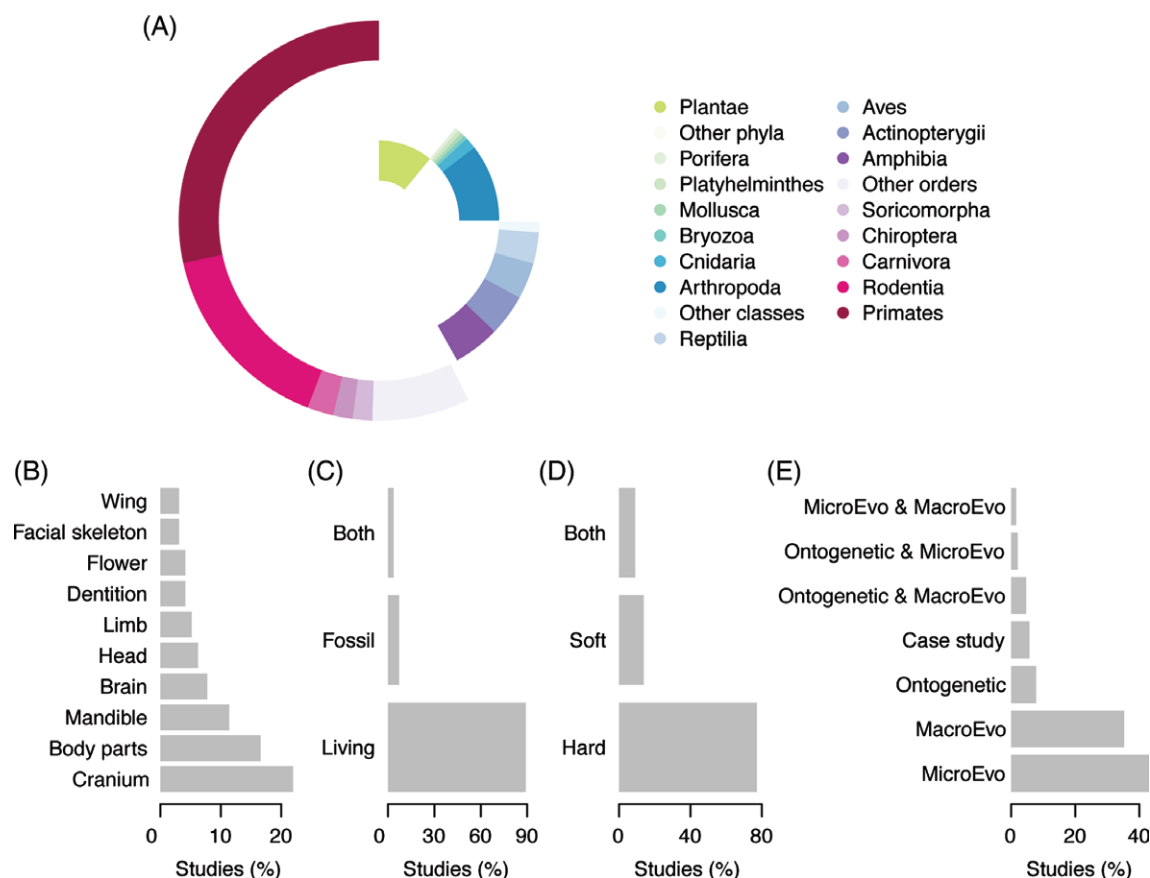
Fig. 2. Morphological modularity research areas shown by (A) taxon, (B) morphological system, (C) tissue (vertebrates only), (D) material, and (E) scale of the study. MicroEvo, microevolutionary scale; MacroEvo, macroevolutionary scale.

whereas the segmented body plan of arthropods (composed of tagmata or metameres) seems particularly relevant to the study of modularity at a morphological level (e.g. Yang, 2001; Yang & Abouheif, 2011; Molet, Wheeler & Peeters, 2012). Similarly, there is limited (<0.5%) or non-existent research in other groups that are often referred as being modular organisms, such as sponges and corals.

Delimiting morphological modules is probably trickier (and more challenging) in the head of vertebrates than in other parts of their body. It has been suggested (Lieberman, 2011*a*) that this occurs because of the presence of more overlapping developmental and functional interactions in the head than in other body parts, which may obscure the patterns of covariation (Hallgrimsson *et al.*, 2009). Nevertheless, the head region is the most-studied morphological structure (Fig. 2B). The majority of articles focus on particular components of the head, such as the cranium (21%), mandible (11%), brain (8%), or dentition (5%); while the head as a whole was considered only in 7% of studies (e.g. Hünemeier *et al.*, 2014; Tsuboi, Gonzalez-Voyer & Kolm, 2014). Only 16% of the articles compared morphological integration within and among different parts of the body (i.e. considering them as individual modules), such as cranial *versus* postcranial skeleton, forelimb *versus* hindlimb, and flowers *versus* leaves. Again, morphological structures

commonly acknowledged for having well-delimited modules, such as the limb of tetrapods (5%), the flower of angiosperms (4%), and the wing of insects (3%) (e.g. Klingenberg & Zaklan, 2000; Hamrick, 2012; Diggle, 2014), are poorly studied compared to the vertebrate head. The preference for head structures does not seem related to answering general questions about the origin and evolution of morphological modularity, but attempts to unravel the morphological organization of a complex structure that fascinates us. Distribution of grant funding to research in this system might also be a plausible reason for this bias.

The literature reviewed shows an over-representation of hard tissues, extant species, and evolutionary scales (Fig. 2C–E). Notably, only the 13% of the vertebrate articles analyse soft tissues, including those that consider the brain. This contrasts, for example, with the importance placed on the developmental and functional differences between hard and soft tissues to explain the morphological evolution of vertebrates (Diogo & Wood, 2013; Richtsmeier & Flaherty, 2013). Hard tissues are sometimes given priority for practical reasons (e.g. ease of handling, allows inclusion of fossils) or are regarded as more evolutionarily stable (i.e. showing less homoplasy) (reviewed in Diogo & Wood, 2013). However, only 10% of studies use fossil materials (7% alone and 3% in combination with extant species), whereas studies on
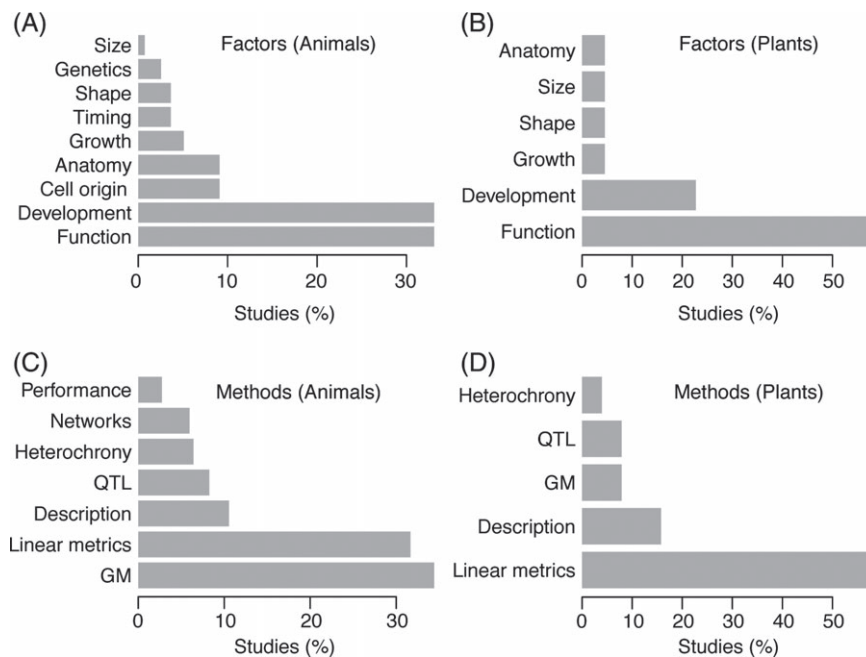
Fig. 3. Patterns in the design of studies of morphological modularity. (A, B) Criteria used to delimit morphological modules in animals and plants. (C, D) Methodological approaches in animals and plants. GM, geometric morphometrics; QTL, quantitative trait loci.

the evolution of the muscular system in primates suggest that the argument that soft tissues are less evolutionarily stable lacks empirical support (e.g. Diogo & Wood, 2011, 2013). Finally, most of the articles reviewed study micro- or macroevolutionary scales (87%), while only 14% study exclusively or partially an ontogenetic scale, despite the importance of development in the study of morphological modularity. Taken together, these findings suggest that we know relatively little about the morphological modularity of soft-tissue systems, or of systems combining hard and soft tissues. Fortunately, there is increasing interest in the study of modularity in soft and hard/soft structures such as the brain, brain/cranium, and bones/muscles (e.g. Richtsmeier *et al.*, 2006; Gómez-Robles *et al.*, 2014; Esteve-Altava *et al.*, 2015*bb*).

(2) Defining, validating, and explaining modules

A typical research article on morphological modularity follows a two-step approach: first proposing an hypothesis of modules according to functional, developmental, genetic, or evolutionary criteria; then, testing this hypothesis using quantitative methods. For example, in studies using morphometrics, an hypothesis of modularity is validated if it conforms to an observed pattern of variational modularity (i.e. some traits covary more among modules than with other traits outside the module). Accordingly, we refer to functional, developmental, genetic, and evolutionary modules depending on the integrating factors at play (for a review of this approach see Klingenberg, 2008).

Function and development are the two most common criteria used to propose testable morphological modules, but their predominance differs between animal and plant

studies (Fig. 3A, B): in animals, development and functional criteria are used alike (34%); in plants, function (61%) is used more often than development (22%). There might be historical reasons for this difference. Animal studies often refer to Olson & Miller's (1958) book *Morphological Integration* and to Cheverud's works published during the 1980s and 1990s analysing patterns of developmental and functional integration in the cranial skeleton (Cheverud, 1996). By contrast, plant studies usually refer to the work of Berg (1960) proposing a modular organization of angiosperms based on reproductive and vegetative functional criteria. This downplay of developmental factors relative to functional factors in plant studies may suggest that development is less important than function in shaping plant modules. Further empirical studies are needed to elucidate this question.

The most common methods used in the literature are related to the quantification of size and shape (i.e. traditional and geometric morphometrics), whereas description, quantitative trait loci, heterochrony, network analysis, and biomechanical performance are less common (Fig. 3C, D). In animals, geometric morphometrics is used slightly more frequently (36%) than linear metrics (31%). In plants, linear metrics (62%) are used much more frequently than geometric morphometrics (8%). Again, this difference might have an historical explanation in the more recent introduction of geometric morphometric procedures in plants than in animals. In the context of morphological modularity, the earliest studies using geometric morphometrics in animals are from the late 1990s (Monteiro & Abe, 1997; Adams, 1998), while in plants they date from the early 2010s (Klingenberg *et al.*, 2012). Finally, it is worth noting that there is a

Table 1. Frequency of factors most commonly used to explain modularity and integration in animals and plants.

	Animals	Plants
Modularity	Development (29.8%)	Function (38.2%)
	Function (27.1%)	Environment (35.3%)
	Genes (11.2%)	Development (14.7%)
	Environment (8.9%)	Genes/phylogeny (5.9% each)
Integration	Function (29.6%)	Genes (25%)
	Development (25.9%)	Development (25%)
	Genes (14.8%)	Function (25%)
	Environment (11.1%)	Growth/environment (12% each)

recent trend to extend the use of methodological approaches previously restricted to the study of one type of morphological structure to the study of other structures. For example, geometric morphometrics has been used recently to analyse modularity of brain shape (Gómez-Robles *et al.*, 2014), while network analysis has been applied to analysis of modularity of head structure (Esteve-Altava *et al.*, 2013, 2015*bb*).

Independent of the method used, only 42% of the articles validated at least one of the hypotheses proposed, the remaining 58% either rejected all hypotheses or found an unexpected result (i.e. not considered in any initial hypothesis). In total, 73% of the articles reported a pattern of modularity in the system studied, while 27% reported that whole-system integration was stronger than modularity (i.e. modules were not identifiable or delimited). Results reporting whole-system integration or modularity were not statistically linked to any organism or methodological approach (Appendix S3). The four leading factors explaining both types of results were functional, developmental, genetic, and environmental. Their relative importance differs between studies of animals and plants, and between studies reporting modularity and integration (Table 1). In animals, function and development are the two factors most commonly used to explain both modularity and integration, followed by genetic and environmental factors. There is no association between modularity or integration and the type of factor used to explain it. By contrast, in plants external factors (functional and environmental) are used most often to explain a pattern of modularity, while internal factors (genetic and developmental) are used slightly more in explanations of integration.

(3) Examples of morphological modules

This section summarizes the morphological modules reported in the reviewed literature for some of the most popular systems: the skeleton of vertebrates (cranium, mandible, and limbs), the brain of primates, the wing of insects, and the body of angiosperms. This is not an exhaustive list or an evaluation of the merits of each hypothesis of morphological modularity proposed, but a glimpse of the modules frequently proposed for each system. The reader will find references to more detailed reviews in each section.

(a) The cranium

The mammalian cranium is the most commonly studied structure studied in the reviewed literature (Fig. 4A). Most authors divide the cranium into various modules, hierarchically nested by developmental and functional interactions (e.g. Makedonska, 2014). Often the cranium is divided into orofacial, cranial base, and cranial vault modules, which derive from the more classic division into face and neurocranium (Moore, 1981). However, the exact boundaries among these modules vary among studies, depending on species analysed, materials available, and methodological approach. Another common modularity hypothesis divides the cranium into oral, nasal, orbital, zygomatic, base and vault modules (Cheverud, 1982), or even smaller modules (e.g. Makedonska, 2014). These modularity hypotheses derive from the functional matrix hypothesis of Moss & Young (1960), which states that skeletal units develop and evolve in response to the functional demands of surrounding soft tissues and cavities. Although some studies have moderated the relative importance of functional matrices (e.g. brain, nasal, and oral cavities) in shaping cranial modularity and morphological variation (e.g. Lieberman, 2011*a*,*b*; Esteve-Altava & Rasskin-Gutman, 2014), the influence of functional matrices is generally acknowledged in craniofacial development. However, there are few studies that evaluate the modularity of the cranium in relation to, or together with, its surrounding soft tissues (e.g. Richtsmeier *et al.*, 2006; Esteve-Altava *et al.*, 2015*bb*).

(b) The mandible

Closely related functionally, developmentally, and topologically to the cranium, the mandible is often studied as a separate morphological structure in studies on modularity (Fig. 4B). According to developmental and genetic criteria, the mandible comprises two modules: an anterior alveolar region and an posterior condylar ramus (Klingenberg, Mebus & Auffray, 2003). This division is also functional because the alveolar module bears the dentition, while the condylar ramus articulates with the cranium and serves as the insertion surface for many masticatory muscles. However, according to functional and evolutionary criteria the mandible can be further sub-divided into five modules: the tooth-bearing incisor zone and the molar zone in the alveolar zone; and the coronoid, condylar, and angular processes in the ramus region (e.g. Ehrich *et al.*, 2003; Renaud, Alibert & Auffray, 2012). Moreover, the dentition can be considered as a module within the jawbone, or as a semi-autonomous system that is further divided into tooth-row modules and tooth modules (e.g. Labonne *et al.*, 2014).

(c) The postcranial skeleton

The study of modularity in the postcranial skeleton has focused mainly on the limbs (Fig. 4C). The limb is commonly divided according to functional and developmental criteria into the stylopod (humerus; femur), the zeugopod (ulna and
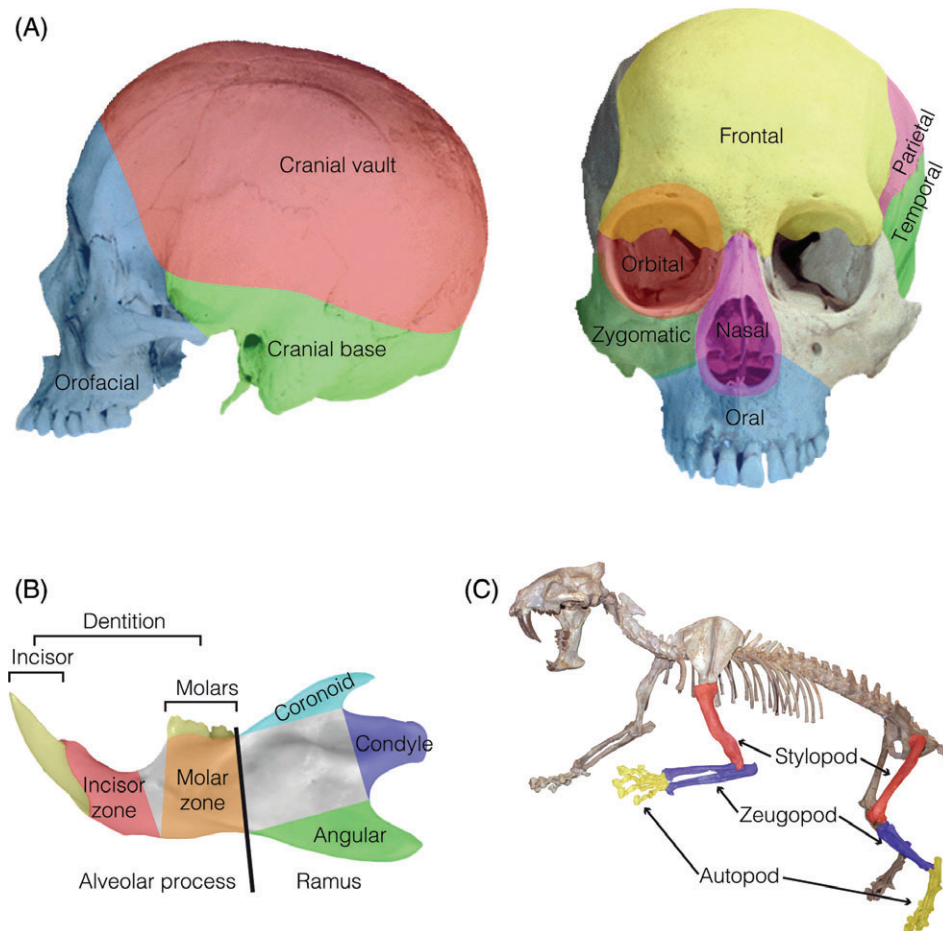
Fig. 4. Morphological modules proposed for the mammalian skeleton. (A) Left, classical division of the cranium into three modules: orofacial, cranial base, and vault. Right, modules proposed by Cheverud (1982) according to the Functional Matrix Hypothesis (Moss & Young, 1960): each module comprises the skeletal units affected by the formation and functioning of each functional matrix of the head (e.g. nasal, oral, and brain). (B) Modules of the mandible illustrated in *Apodemus* sp. (Rodentia: Mammalia). The alveolar process and the ramus are the two main divisions of the jawbone. Additionally, various regions of the mandible are considered morphological modules according to their development, ossification, as well as their function related to attachment of muscles, articulation, and tooth bearing. The dentition is often studied as a separate structure, with each tooth series as an independent module. (C) Modules of the tetrapod limb illustrated in *Hoplophoneus dakotensis* (Carnivora: Mammalia): the autopod, zeugopod, and stylopod are the three modules of the limb, with the girdle sometimes considered as an additional module. Image credits: original photograph of the human cranium from eSkeletons.org; original photograph of the *Hoplophoneus* skeleton by Rama (source: Wikimedia commons).

radius; tibia and fibula), and the autopod (wrist and fingers; ankle and toes). Various studies approach the modularity of limbs by comparing patterns of morphological integration among these three units in the same limb, between left and right limbs, or between forelimb and hindlimb (see also Goswami *et al.*, 2014; Martín-Serra *et al.*, 2015). A less-common approach is the study of modularity within a single bone, such as the scapula (Young, 2004), the humerus (Árias-Martorell *et al.*, 2014), and the tibia (Tallman *et al.*, 2013).

(d) *The brain of primates*

The morphological division of the brain is commonly related to the embryonic origin of each of its parts: the forebrain (telencephalon and diencephalon), the midbrain (mesencephalon), and the hindbrain (metencephalon and myelencephalon) (Redies & Puelles, 2001). Alternatively, the brain is organized into left and right hemispheres, and these, in turn, into regions or lobes: frontal, parietal, temporal, and occipital (Marrelec *et al.*, 2008). Brain modules are also studied in relation to their functioning, as regions that interact to perform a given task (i.e. functional integration) in normal and pathological conditions. More recently, Gómez-Robles *et al.* (2014) studied the morphological modularity of the brain at larger and finer scales, using geometric morphometrics to compare the morphological integration of various divisions of the brain according to functional, structural, evolutionary, and developmental criteria (Fig. 5).
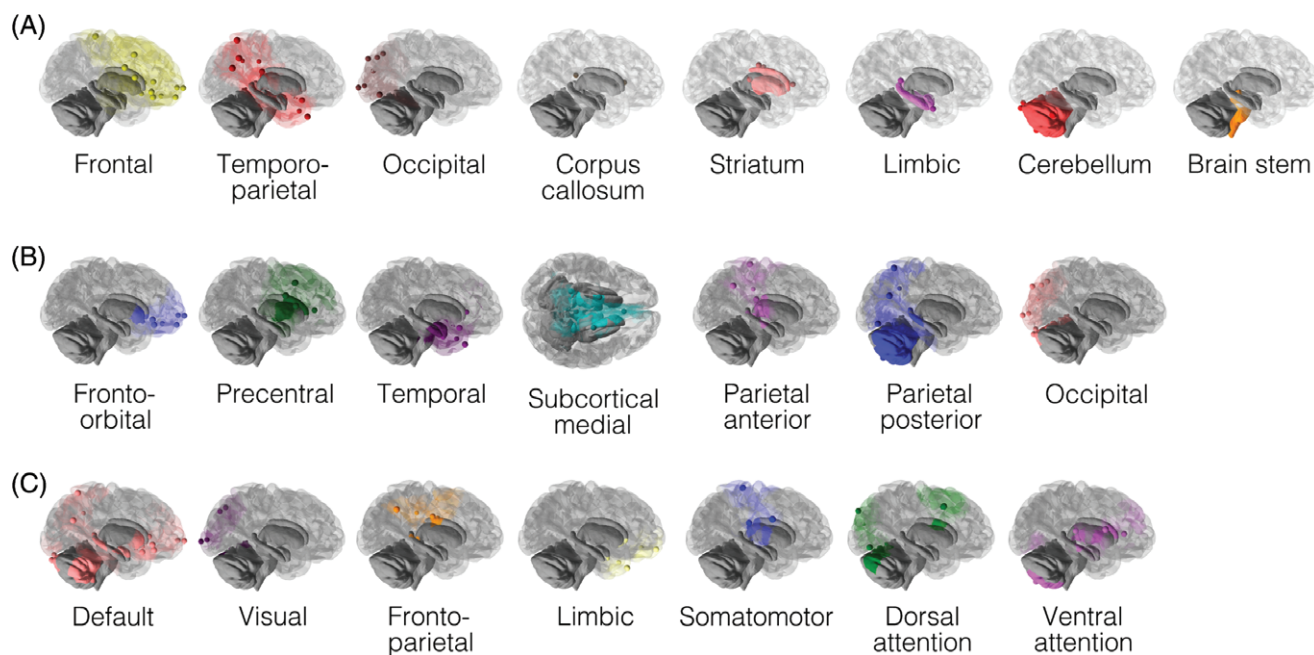
Fig. 5. The modules of the brain illustrated in *Homo sapiens*. The image shows different modularity hypotheses of the brain according to (A) evolutionary and developmental criteria, (B) structural criteria, and (C) functional criteria. Modified with permission from Gómez–Robles *et al.* (2014) © NPG.

(e) The insect wing

Arthropods have a clearly recognizable modular body plan (Wagner, 1990), and yet the study of this group has focussed mainly on the insect wing. The most common division of the wing is into two modules: anterior and posterior (Klingenberg *et al.*, 2001) (Fig. 6A). In insects with two pairs of wings, the forewing and the hindwing also have been reported as representing two different modules. Other geometric divisions, based on the wing patterns, have been used to describe the wings of some insects (e.g. the nymphalid ground plan; see Suzuki, 2013).

(f) Angiosperms

The gross morphology of flowering plants shows often a modular division into vegetative parts (roots, stems and leaves) and reproductive parts (flowers) (Fig. 6B). The distinction between vegetative and reproductive modules has its origin in the work of Berg (1960) on phenotypic pleiades (Conner & Lande, 2014). Current research on plant modularity focuses on uncovering more precisely the contribution of genetic and developmental constraints, and of natural selection (in particular, that related to pollination), in the organization of phenotypic integration (e.g. Murren, 2002; Rosas-Guerrero *et al.*, 2011). In general, most of our knowledge on plant modularity comes from the study of flowers; in the reviewed literature, the results suggest a division of the flower into functional and developmental modules, as well as into pollen-transfer and pollinator-attraction modules. The modularity of the flower has been recently reviewed in detail by Diggle (2014).

(4) Future research into morphological modularity

The panoramic view presented herein calls into question the common assumption that modularity is widespread in all body plans, because most of our knowledge regarding morphological modularity derives from the study of a few over-represented groups (model organisms and humans). Directing our attention to under-represented organisms will fill this knowledge gap and also has the potential to reveal previously unknown mechanisms guiding the establishment of morphological modules. A similar argument can be made for the systems and materials of study (Section III.1); most of our knowledge comes from hard tissues in vertebrates, thus modularity patterns in other soft tissues (except perhaps the brain) are less well known (Section III.3). Studying morphological modularity in under-represented groups and systems requires a more-inclusive definition of morphological modularity, such as the minimum definition (Section I.1) used herein: a group of body parts that are more integrated (i.e. interact more) between themselves than they are to other parts outside the group. This definition applies, for example, to sponges as well as to vertebrates, and to soft tissues as well as hard tissues. Other methods are available to explore modularity in addition to morphometrics, such as anatomical networks. Combining these will help understand how modularity is expressed at a morphological level; for example, combining morphometrics and anatomical network approaches can be used to test how topology affects shape, and *vice versa*, in making the heterogeneous patterns of form that we identify as modules (some studies have already begun to do this, see e.g. Perez *et al.*, 2009; Suzuki, 2013). Finally, there is a need to discriminate more clearly between
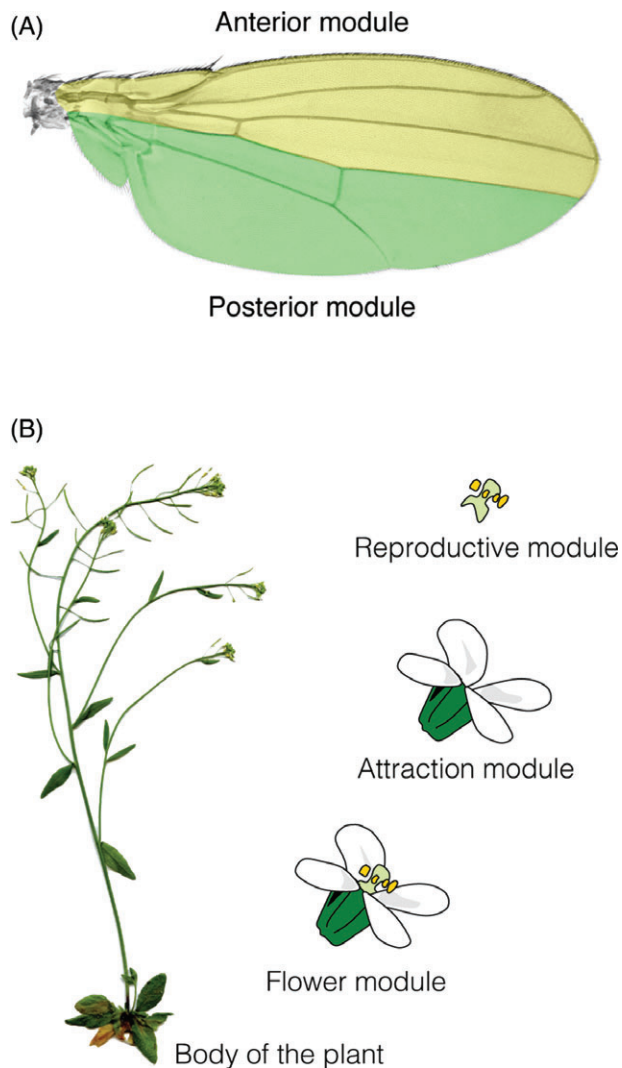
Fig. 6. (A) Modules of the wing of insects illustrated in *Drosophila suzukii* (Diptera: Insecta). The wing comprises an anterior and a posterior module derived from different developmental compartments. (B) Modules of flowering plants illustrated in *Arabidopsis thaliana* (Brassicales: Eudicots). Flowering plants are often divided into vegetative parts (roots, stems and leaves) and reproductive parts (flowers). In turn, the flower is divided into parts related to the attraction of pollinators and parts related to the pollination itself. Image credits: original photograph of the wing by Martin Hauser (source: Wikimedia commons); original photograph of the plant by Lot Nature (source: www.lotnature.fr); original drawing of the flower by Yvon Jaillais (source: www.ens-lyon.fr/RDP/SiCE/Resources.html).

developmental and functional mechanisms determining (i.e. explaining) the formation of morphological modules. The results of this review suggest that all too often studies fail to discriminate between internal and external factors as the causal agents of modularity. We must acknowledge however that in nature developmental and functional factors are intimately intertwined in shaping organismal form. However, experimental studies in the laboratory now allow us to investigate in more detail the relative influences of internal *versus* external factors (or their indissoluble integration, if it is so) in the formation of morphological modules.

IV. CONCLUSIONS

(1) The findings of this systematic review identified certain biases that must be overcome in order to reveal a new picture of how morphological modularity develops and evolves in complex living beings.

(2) The reviewed evidence suggests that our knowledge about morphological modularity is biased towards the study of mammals (in particular, *Homo* and *Mus*), whereas plants and arthropods are under-represented despite having an *a priori* well-defined modular body plan. This bias raises questions regarding the ubiquity of morphological modularity, because we lack first-hand evidence for many body plans. More studies of these under-represented organisms (including non-model organisms) and body plans would help to understand whether, as it is generally assumed, modularity is widespread in multicellular eukaryotes.

(3) Although the head of vertebrates has been well studied, muscles and other soft tissues (except the brain) often are not considered. This reinforces a bias towards hard tissues that fails to consider the impact of muscles in shaping the head's modularity. Hence, we know relatively little about the morphological modularity of systems composed only of soft tissues, or of systems combining hard and soft tissues.

(4) Most (73%) studies report the presence of morphological modules, whereas only 27% revealed that integration among parts was stronger than modularity. This indicates that, even though modularity might be ubiquitous, the degree of modularity *versus* integration varies depending on the morphological system studied, as expected if one considers a hierarchical organization of the body. Studies reporting whole-system integration or modularity were not related to any particular taxonomic group or methodological approach.

(5) Factors explaining modularity and whole-system integration vary between animals and plants. In animals, developmental and functional factors are used to a similar extent to explain the presence or absence of morphological modules. In plants, function and environment (external factors) are most frequently used to explain a modular phenotype, while development and genes (internal factors) tend to be used to explain whole-phenotype integration.

V. ACKNOWLEDGEMENTS

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VII. SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article.

Appendix S1. Data set evaluated in the systematic review.

Appendix S2. R script used to analyse the data set and create Figs 1–3.

Appendix S3. Detailed results of the analysis of the data set.