The golden mean: A systems biology approach to developmental language disorders

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EL JUSTO MEDIO: LOS TRASTORNOS DEL LENGUAJE LIGADOS AL DESARROLLO DESDE LA ÓPTICA DE LA BIOLOGÍA DE SISTEMAS

THE GOLDEN MEAN: A SYSTEMS BIOLOGY APPROACH TO DEVELOPMENTAL LANGUAGE DISORDERS

ABSTRACT: Current typologies of developmental language disorders are mostly based on symptomatic criteria. Nonetheless, they often fail to categorize and characterize patients unambiguously, essentially because of the widespread problems of comorbidity and heterogeneity. Likewise, they usually fail to incorporate etiological factors in a precise way. These shortcomings are expected to impact negatively on therapies and the recovery of patient’s abilities. This paper advocates a systems biology approach to developmental language disorders, aimed to disentangle how the myriad of biological factors involved (at the bottom) interact complexly to regulate language development and processing (at the surface). In particular, it advocates a classification of disorders based on intermediate-level components, like brain oscillations. This fresh approach to the etiopathogenesis of developmental language disorders, which is more biologically motivated and more theoretically grounded, should allow identify robust endophenotypes of these conditions, that can be used as reliable hallmarks for an earlier and more accurate diagnosis.

KEY WORDS: developmental language disorders; symptomatology; aetiology; clinical linguistics; systems biology; brain oscillations; endophenotypes; evo-devo.

RESUMEN: Las tipologías de los trastornos del lenguaje ligados al desarrollo se basan fundamentalmente en criterios sintomatológicos. No obstante, frecuentemente son incapaces de categorizar adecuadamente a los pacientes, fundamentalmente debido a la heterogeneidad y la diversidad típicas de los trastornos, y a la comorbilidad que se advierte entre ellos. Asimismo, dichas tipologías no contemplan como debieran la naturaleza de los factores etiológicos que explican cada trastorno. Estas circunstancias pueden condicionar negativamente el tratamiento de los afectados. En este artículo se defiende una caracterización de estos trastornos desde la óptica de la biología de sistemas, que busca discernir la manera en que los factores biológicos implicados interactúan de forma compleja para explicar el desarrollo y el procesamiento anómalos del lenguaje. En concreto, se defenderá una clasificación basada en componentes biológicos intermedios, en particular, las oscilaciones cerebrales, que se espera que constituyan además endofenotipos más fiables, que permitan diagnósticos más exactos y tempranos.

PALABRAS CLAVES: trastornos del lenguaje ligados al desarrollo; sintomatología; etiología; lingüística clínica; biología de sistemas; oscilaciones cerebrales; endofenotipos; evo-devo.

SUMMARY: 1. Introduction. 2. Clinical linguistics: a messy scenario. 3. A paradigm shift in clinical linguistics: Brain rhythms: bridging genes to language. 5. Conclusions and future prospects.

SUMARIO: 1. Introducción. 2. Lingüística clínica: no todo está claro. 3. Hacia un cambio de paradigma en lingüística clínica. 4. Los ritmos cerebrales como puente entre los genes y el lenguaje. 5. Conclusiones y áreas de interés para la investigación futura.

SUMMAIRE: 1. Introduction. 2. Linguistique clinique: un scénario compliqué. 3. Un changement de paradigme en linguistique clinique. 4. Rythmes cérébraux: relier les gènes au langage. 5. Conclusions et perspectives d’avenir.

Fecha de Recepción 05/02/2019
Fecha de Revisión 19/03/2019
Fecha de Aceptación 10/05/2019
Fecha de Publicación 01/12/2020 http://doi.org/10.25267/Pragmalinguistica.2020.iextra2.02
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1. INTRODUCTION

This paper is aimed to discuss new theoretical approaches to the nature of developmental language disorders that can account for many of the recent findings about their biological nature in the domains of genetics, brain physiology, and behaviour. Hopefully, these new models will help physicians, speech therapists, and clinical linguists to better interpret the relevance of their findings, improve their understanding of the etiology and symptomatology of disorders, and ultimately, achieve earlier and more confident diagnoses of developmental language disorders, as well as more efficient therapies. On paper, clinical categories like dyslexia or specific language impairment refer to cognitive disorders in which only language is impaired and that can be differentiated from other similar categories at all levels: linguistic, cognitive, neurobiological, and genetic. However, things are usually less clear-cut and more difficult to handle, essentially, because the boundaries between disorders are blurred at all those levels. This circumstance is expected to impact negatively on the diagnosis and the therapeutic approaches aimed to ameliorate the symptoms and deficits associated to these conditions. This problem is not easy to fix. The take-home lesson of the paper will be that clinical linguistics will benefit from a shift of focus in the line of the ongoing evo-devo revolution in biolinguistics, and more generally in biology: instead of relying on the analysis of the phenotype in the adult state, more attention should be paid to developmental dynamics in pathological populations across all levels of biological complexity, from genes to language deficits. As also discussed, this should allow to find more reliable endophenotypes of these conditions, that is, disorder-specific biological markers of the disease. In the paper, brain oscillations will be highlighted as the most promising of such endophenotypes.

2. CLINICAL LINGUISTICS: A MESSY SCENARIO

As noted above, things for clinical linguists and speech therapists are not usually crystal-clear. To begin with, patients commonly show symptoms that are compatible with more than one disorder (linguistic or not linguistic by nature), to the extent that comorbidity is a frequent outcome of clinical

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1 This work was supported by funds from the Spanish Ministry of Economy and Competitiveness (grant number FFI2016-78034-C2-2-P [AEI/FEDER, UE] to Antonio Benítez-Burraco.
practice. At the same time, people suffering from a particular disorder usually exhibit linguistic (dis)abilities that are pretty variable. In order to apprehend this variability different subtypes of the same disorder are usually posited, in which one aspect of language is claimed to be more impaired than others. Importantly, problems with language at the surface, so to speak, are only indirectly related to the attested cognitive deficits at the bottom, as one underlying cognitive deficit can impact on many aspects of language, whereas different cognitive deficits can coincide on a common set of problems with language. This circumstance contributes to increase the variability of the symptoms and to make the categorization of disorders more troublesome. Accordingly, different subtypes of a particular disorder (or even different disorders) can result from a differential manifestation of the same (broad) cognitive deficit, hence the alleged heterogeneity and/or comorbidity. But if different deficits (specific or not to language) contribute to the same disorder, it is possible as well that each subtype of a particular disorder results from a different prevailing deficit. Figure 1A summarises this complex scenario.

Figure 1: A messy scenario for clinical linguistics at the phenotypical level. A. The links between cognitive deficits and language problems in developmental language disorders are not straight or univocal. B. Language problems cannot be easily linked to aspects of linguistic theory (left). Moreover, they commonly change thorough development.

Another important concern is that, very frequently, problems with language in the affected people concern to quite broad aspects of language,
to the extent that they do not match units, levels, features, or operations that are important for modern linguistic theory (Figure 1B, left). As a consequence, clinical typologies are sometimes weird for linguists. For instance, according to some views (e.g. Rapin and Allen, 1983) there exists a syntactic-pragmatic subtype of specific-language impairment. But linguists carefully differentiate between the knowledge needed for assembling words into sentences (syntax) and how this knowledge is put into use or communicating in effective ways (pragmatics). Actually, for most linguists (and for most neurolinguists indeed) pragmatics involves many other abilities besides our knowledge of language.

Finally, consider that the clinical profile of patients usually changes throughout development, up to the point that the affected subjects can “switch” from one subtype to another of the same disorder as they grow (Figure 1B, right). As a corollary, one cannot assume that the problems with language in the adult state will be the same as those observed during childhood (and vice versa).

Comorbidity, heterogeneity, and variability are observed at the neurobiological level too (Figure 2). Accordingly, the brain areas found affected in one disorder can be found impaired in people suffering from a different disorder. Moreover, it is frequently observed that the dysfunctional regions give rise to mixed symptoms. Overall, it is not clear whether the involved brain areas are multifunctional by nature or perform instead some basic computations that are recruited for language and for other cognitive processes. Lastly, it commonly happens that the boundaries of the affected areas do not overlap across patients.

Figure 2: A messy scenario for clinical linguistics at the neurobiological level.

Things are not easier to interpret at the molecular level. Different candidate genes and risk factors for developmental language disorders have...
been identified to date. However, it is not one but many genes that usually contribute to each disorder. Additionally, it is not one but several pathogenic variants that can be found for each of these candidate genes, with some others contributing as well to the language abilities of the neurotypical population. Importantly, the same mutation in the same gene can cause the disorder in some individuals, but not in others. Conversely, affected people can carry no pathogenic variant of any of the candidate genes associated to the disorder. What is more, the same mutation in the same gene can give rise to different disorders in different subjects, to the extent that candidate genes for a particular disorder are frequently invoked as candidates for several other clinical conditions. Finally, it is frequently observed that mutations in genes encoding proteins that are functionally related (if one regulates the expression of the gene encoding the other) can give rise to different disorders in different people and/or environments (Table 1).

Table 1: A messy scenario for clinical linguistics at the genetic level. Polygenism refers to the circumstance that disorders are frequently caused by mutations in more than one gene. Variants of a gene are called polymorphisms. Penetrance refers to the variable effect of a particular mutation on the language phenotype, whereas phenocopy refers to the presence of pathological symptoms in absence of pathogenic polymorphisms. Genes are pleiotropic if they contribute to different biological processes in different body regions.

The advent of the so-called “-omics revolution” in Biology has turned this complex scenario even more complex. On the one hand, the amount of biological data about disorders has grown exponentially. On the other hand, we have learnt that there are additional levels of biological complexity that need to be explored if we want to gain an accurate view of the real nature of disorders. Accordingly, epigenetic changes, modifications of protein networks, alterations of signalling pathways, abnormal patterns of neuronal assembly, or aberrant patterns of neuronal synchronization need to be considered on a par to gene mutations, abnormal neuroimaging results, or language deficits (Figure 3). Actually, as we will argue in the last part of the
paper when discussing brain oscillations, it might well be that the specificity of language in cognition, and hence, the idiosyncrasy of developmental language disorders, that we cannot find at the genetic or the phenotypical levels, can be found instead at some of these new levels of biological complexity.

![Figure 3: Levels of biological complexity that need to be considered in any comprehensive characterization of language (and of developmental language disorders) from a biological perspective (reproduced from Benitez-Burraco and Murphy, 2014; figure 4).](image)

### 3. A PARADIGM SHIFT IN CLINICAL LINGUISTICS

If we consider our discussion in section 3 above, it seems that clinical linguistics, which has traditionally focused on the cognitive evaluation of patients and the analysis of corpora of disordered language, confronts a
triple challenge. First, it needs to consider additional types of evidence, as provided by other areas of research also interested in developmental language disorders, like neuroscience or genetics (this is the challenge of *multidisciplinarity*). Second, it needs to rely on new research methodologies and tools, which are sometimes difficult to understand and use, like neuroimaging facilities (this is the challenge of *technification*). Third, it needs to improve current etiological accounts of language disorders. For this, it is not enough with considering fresh data about their biological foundations, but also fresh models of development and evolution as currently discussed by biological sciences (this is the challenge of *theorization*). In truth, one possible (and perhaps the only possible) way of properly addressing these three challenges is adopting a systems biology approach to developmental language disorders. Contrary to other approaches to biological facts, which are reductionists by nature, systems biology aims to study the dynamics of cellular and organismal function with a focus on properties of the whole system (Kitano, 2002). Systems biology as adapted to clinical linguistics would be thus aimed to characterise, from a holistic perspective, the complex interactions among myriads of biological components that take place within the brain of people with disorders when processing language, as well as the emergent properties resulting (or failing to result) from such interactions. Among others, this approach is expected to circumvent the shortcomings and limitations of current typologies of developmental language disorders. This is why in this paper we have put the focus on the last one of the former three challenges, namely, the challenge of theorization.

Current typologies of language disorders are based either on symptomatic criteria or on etiological criteria. Typologies based on symptoms often fail to categorize and characterize patients unambiguously, essentially because of the widespread problem of comorbidity and heterogeneity, as discussed above. Also, they usually fail to incorporate etiological factors in a disorder-specific way. As discussed, pathogenic gene variants, dysfunctional brain regions, or even abnormal cognitive processes can be usually associated to more than one clinical condition. This is an important concern also for etiological classification of disorders. For instance, concerning genes, because it seems now that complex diseases entail an abnormal expression pattern of many if not most of the genes expressed in the body (Boyle *et al.*, 2017), we should expect that language disorders entail as well an abnormal expression pattern of many if not most of the genes expressed in the brain. Accordingly, clinical conditions should be better characterised in terms of whole-brain transcriptomic profiles, that we can expect to be disorder-specific, instead of in terms of gene mutations, that we should expect to be associated to more than one disorder. Still, etiological classifications fail to explain why only a bunch of distinctive symptomatic profiles (i.e. clinical conditions) result from the interaction of thousands of potential etiological factors, some of them being altered and some of them being intact, with most
if not all being shared across disorders that exhibit, as noted, different symptomatic profiles.

This messy scenario (as we labelled it in the previous section of the paper) is easier to interpret if we rely on eco-evo-devo theories in biology, which build on the deep link between the environment, development, and evolution. According to this approach, language resulted from minor changes in the developmental path of the hominin brain in response to changes in the environment in which our ancestors lived. And it is the most recently evolved components of human cognition which are expected to be the most sensitive to the deleterious effect of developmental perturbations resulting from environmental, because of their reduced resilience. This circumstance explains two widespread outcomes of clinical linguistics. First, although as noted, the etiology of disorders is quite diverse, some deficits are shared by nearly all conditions and they usually pertain to morphophonology and to other highly demanding computational tasks, like agreement. These aspects impaired in most disorders concern to the interface between basic cognitive blocks (sounds and syntax, syntax and semantics, and the like). Whereas the former are very robust after millions of years of stabilizing selection (and as a consequence, they are not usually found impaired in most disorders), the interfaces evolved very recently and rely on less resilient neural networks, being thus more sensitive to damage (and as a consequence, they are usually found impaired in most disorders).

Second, although as also noted the number of factors potentially contributing to developmental language disorders is large, the number of disorders is far fewer. Accordingly, the disorders described by clinical linguistics could be the only possible phenotypes resulting from the impairment of the myriad of factors involved in brain development. In eco-evo-devo theories the finite set of phenotypes allowed during development is construed as a morphospace or adaptive landscape, with each phenotype being a definite area within the whole space (Arnold et al., 2001; Erwin, 2017). Putting this differently, developmental dynamics canalizes development through a restricted set of ontogenetic paths. As a consequence, what we label the neurotypical language brain could be viewed as the outcome of a successful canalization of the otherwise widespread developmental noise (that is, gene mutations, minor brain anomalies, and the like). In turn, what we call developmental language disorders could be viewed as suboptimal canalizations of more severe developmental disturbances (like deleterious gene mutations, substantial brain damage, etc.).

What we need to determine are the best parameters defining the language morphospace. Consider, as an informative example, the shells of ammonites and nautili. Similarly to language disorders, the number of different shell forms was small: coiled, uncoiled, and helical. Nonetheless, the shell morphology depends on two parameters, namely, rib expansion rate and rib coiling tightness, that change continuously (Moulton et al., 2015), similarly to what happens with the etiological factors of language disorders. One
possibility is relying on gene expression profiles in the brain: we can confidently expect that different disorders are associated to different, disorder-specific abnormal profiles, in the line of the omnigenic hypothesis of complex diseases. Nonetheless, in the last section of the paper, we will highlight brain rhythms as the best candidate for properly defining the morphospace of language growth in the species, either pathological or neurotypical.

4. Brain rhythms: bridging genes to language

Brain oscillations are of great interest for several reasons. First, they are primitive components of brain function. Second, we expect them to be associated with (and actually, to give rise to) some computational primitives of language, thus allowing to understand (and not just to localize) brain functions. As famously noted by David Poeppel (Poeppel and Embick, 2005), current neurolinguistic studies suffer from two crucial shortcomings. On the one hand, they rely on broad conceptual distinctions (syntax vs. semantics, morphology vs. syntax, etc.), which involve multiple neural components, computations, and representations. On the other hand, the basic elements and functions of language as posited by linguistic theory do not match the basic components and processes of the brain as identified by neuroscience. It is then urgent to spell language in appropriate computational elements that can be processed by the brain in real time. We regard brain rhythms the most promising of such elements. For instance, as shown in Figure 4, the assignment of language-relevant features, like Tense and Case, can be satisfactorily interpreted as the embedding of high frequency oscillations inside oscillations operating at a slower frequency. Similarly, some rhythmic features of speech have been successfully related to specific brain oscillations (e.g. Meyer, 2018 among many others). A third reason is that the hierarchy of brain oscillations has remained remarkably preserved during mammal evolution. Not surprisingly, the human-specific pattern of brain activity accounting for language can be linked to the oscillatory signature of the primate brain. Specifically, the emergence of the human language oscillome (that is, the phasal and cross-frequency coupling properties of neural oscillations related to language) seemingly re-shaped the oscillome we inherited from our primate ancestors (Murphy, 2016). A final, but important reason too is that each cognitive disorder exhibits a disorder-specific abnormal oscillatory profile. This is of particular interest for clinical linguistics: because brain rhythms are highly quantifiable and heritable traits, they might be potentially employed as confident biomarkers or endophenotypes of developmental language disorders. For instance, people with autism spectrum disorders (ASD) typically exhibit a gamma band dysfunction (Port et al., 2015).
Figure 4: An idealised schema showing the links between some language-relevant features and specific brain rhythms (reproduced from Murphy and Benitez-Burraco, 2017; figure 2)

Nonetheless, if we really wish to use these abnormal oscillatory profiles as reliable biomarkers or endophenotypes of language disorders, we first need to map these disorder-specific patterns to the language deficits that are also typical of each disorder. Pretty obviously, this translational effort should also result in a better understanding of the causes of the language deficits found in each condition, particularly, of the effect of gene mutations. Fortunately, this translational effort has proven to be feasible. Accordingly, language deficits observed in conditions like ASD, schizophrenia (SZ), or developmental dyslexia (DD), can be explained in terms of aberrant changes in the normal oscillatory activity of the brain (see Benitez-Burraco and Murphy, 2016; Murphy and Benitez-Burraco, 2016; Jiménez-Bravo et al., 2017, respectively, for details). Just to put one example, neurotypical subjects process speech, γ oscillations correspond to phonetic features and are involved as well in the access to stored templates from memory. As a consequence, the degraded γ and θ synergy found in people with ASD may explain the problems that they experience with speech perception, tone recognition, and parsing phonemic representations.

More importantly, some candidate genes for these conditions can be confidently associated to specific brain rhythms. In some cases, it is even possible to draw bridging links between all the involved biological levels, from gene mutations to abnormal brain oscillations to language deficits (see Murphy and Benitez-Burraco, 2018a). To put another example: as shown in Figure 5, ZNF804A is a gene that encodes a zinc finger binding protein. This gene is highly expressed in the hippocampus and the neocortex, particularly during late embryonic development. The hippocampus is a source of θ bands, which play a major role in the coordination of distributed cross-cortical activity (in particular, the activity in the prefrontal cortex). Because of their involvement in working memory, as a filter that imposes memory-related rules, and because of the role of the hippocampus in the transformation of individual experiences into semantic structures such as maps and schemas, hippocampal θ is expected to explain core aspects of language processing, both syntactic (like the “chunking” of syntactic objects) and semantic (like category fluency). Pathogenic polymorphisms of ZNF804A...
have been related to semantic problems in subjects with SZ. Additionally, significant decreases in the coactivation of the right hippocampus within the whole hippocampal network, as well as decreases in intrahippocampal θ band have been found in risk homozygotes for one variant of this gene. Interestingly, people with this risk allele show a greater coactivation of the hippocampus and the prefrontal cortex (specifically, the superior frontal gyrus). Likewise, several polymorphisms of ZNF804A have been associated to verbal deficits in people with ASD, who exhibit a reduced expression of the gene in several brain areas, like the anterior cingulate gyrus.

![Figure 5: The motivated links between mutations in ZNF804A, abnormal brain oscillations, and language deficits in ASD and SZ (reproduced from Murphy and Benítez-Burraco, 2017; figure 4)](image)

Just to put a last example: as illustrated by Figure 6, GRIN2A is a gene that encodes the subunit 2A of the N-methyl-D-aspartate (NMDA) receptor, which plays a key role in long-term potentiation, important for memory formation and learning. This effect is seemingly due from its regulation of γ
oscillation formation and modulation. Mutations in GRIN2A are found in people suffering from different types of epilepsy-aphasias (like rolandic epilepsies or Landau-Kleffner syndrome). Specifically, they are associated with errors in articulation and with problems with pitch and prosody, which pertain to the syntax-phonology interface. In turn, these deficits can be tracked to an abnormal $\gamma$ activity, involved in the processing of fast-rate phonemic and syllabic information.

Figure 6: The motivated links between mutations in GRIN2A, abnormal brain oscillations, and language deficits in SZ and epilepsies. Here, ‘genome’ refers to the set of genes related to brain rhythms that are relevant for language processing, ‘transcriptome’, to their RNA products, and ‘proteome’ to the proteins they encode. ‘Toponome’ refers to the whole set of codes of proteins and other biomolecules found in the cell surface, whereas ‘organome’ refers to the set of cell signalling molecules involved in cell and organ crosstalk. ‘Cytome’ refers to the collection of different cell types of the organism. ‘Connectome’ refers to the wiring of brain areas involved in language processing. ‘Dynome’ refers to the brain dynamics underlying (and supporting) this processing. ‘Cognome’ refers to the basic cognitive operations underlying language (and in this case, speech processing). Finally, ‘phenome’ refers to the discrete, language-specific activities (in this case, phonological and phonetic aspects of speech) (reproduced from Murphy and Benitez-Burraco, 2018a; figure 6).
Interestingly, most of the candidates for developmental language disorders that also play a role in brain rhythmicity are functionally interrelated and map on particular regulatory pathways, cell types or functions, as well as facets of brain development and function of relevance for language processing, particularly through dopaminergic, GABAergic and glutamatergic synapses. Interestingly too, they are believed to exhibit a distinctive, disorder-specific pattern of abnormal up and downregulation in the brain of patients, which contributes to bridge mutations to abnormal oscillations to aberrant language features. Notice that the specificity of the molecular signature of each disorder relies not on the set of genes involved, which are essentially the same, but on their expression patterns in each brain region, which is different in each condition.

Finally, and perhaps not surprisingly, it is important to note that several of these genes that are responsible for basic aspects of the oscillatory activity of the brain relevant for language processing show differences in their methylation status with Neanderthals (Murphy and Benítez-Burraco, 2018b). Pretty obviously, we cannot track the oscillatory activity of the brain of extinct hominins, but from differences in methylation maps we can infer differences in the expression pattern of genes and ultimately, differences in cognitive functions important for language. In summary, because of this bridging role between genes (at the bottom) and language features (at the surface), both developmentally and evolutionarily, brain rhythms can be the biological level at which the specificity of language (and of language disorders) emerges... the golden mean, just to say.

5. CONCLUSIONS AND FUTURE PROSPECTS

Decades of research on language disorders have demonstrated that besides genes external factors also contribute significantly to the emergence of these conditions. This is another reason why a systems biology approach to developmental language disorders (or an eco-evo-devo clinical linguistics, which is quite the same) is worth pursuing. Systems biology construes organisms as open systems in contact with their environment and it has implemented the needed tools for properly capturing how these interactions affect development (this would be the eco side of eco-evo-devo). To put just one example. Our microbiota (and more generally, the gut-brain cross-talk) has been found to contribute to important aspects of brain development and function. Increasing evidence suggests as well that alterations of the gut-microbiota axis disturb neuronal networks involved in emotional and social responses by people with neurodevelopmental disorders, seemingly contributing to the observed deficits in these domains. Although mechanistic insights are still pending, it is clear that a systems biology approach can result in findings of clinical relevance. The same can be said, specifically, of developmental language disorders.
It is pretty obvious that the research outlined in this paper has a practical side too. If we succeed in this translation of language dysfunctions into disorder-specific patterns of brain anomalous oscillations, we might be able to diagnose developmental language disorders earlier and in more accurate ways. Several complementary lines of future research are of particular interest for improving this systems biology (or eco-evo-devo) approach to developmental language disorders. First, we need to disentangle the molecular mechanisms that channel (and fail to channel) variation at all levels of biological complexity. Second, we need to improve eco-evo-devo-friendly depictions of the modularization of the disordered brain. Third, we should optimize our current models of the linguistic ontogeny in people with disorders. Finally, we should pay attention to emergent properties of language (and to properties that fail to emerge), because language is undoubtedly a complex system and because many properties of complex systems are emergent by nature.

In summary, we regard categorizations and descriptions of developmental language disorders based on intermediate-level components (particularly, on brain oscillations) more biologically motivated and more theoretically grounded than others (particularly, those currently used by clinical linguists, which rely either on symptoms or on causes). Accordingly, they are expected to provide more robust endophenotypes of developmental language disorders that can be used for an earlier and more accurate diagnosis of these conditions. A next step will be applying this new paradigm to the characterization of acquired language disorders. Although they result from the selective damage of specific brain areas in the adult brain, their distinctive symptoms are expected to emerge as well from the disturbance of multiple factors.

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