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The Immune Syntax Revisited: Opening New Windows on Language Evolution

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Recent research has added new dimensions to our understanding of classical evolution, according to which evolutionary novelties result from gene mutations inherited from parents to offspring. Language is surely one such novelty. Together with specific changes in our genome and epigenome, we suggest that two other (related) mechanisms may have contributed to the brain rewiring underlying human cognitive evolution and, specifically, the changes in brain connectivity that prompted the emergence of our species-specific linguistic abilities: the horizontal transfer of genetic material by viral and non-viral vectors and the brain/immune system crosstalk (more generally, the dialogue between the microbiota, the immune system, and the brain).

Keywords: language evolution, HGT, microbiome, immune system, brain, skull, globularity, externalization

INTRODUCTION

Hauser et al. (2002) hypothesized that our Faculty of Language may be decomposed into a core computational system (the narrow faculty of language or narrow syntax, NS) and two interface devices; a conceptual-intentional system and an externalization system. In their view, only the NS was specific to humans. The emergence of NS is thought to be bound to a brain rewiring that gave rise to a domain-general computational ability, either a recursive capability (Hauser et al., 2002), or one for combining conceptual units that belong to distinct "core knowledge systems", presumably linked to the changes that brought about our globular brain and braincase (Spelke, 1994, 2000, 2003; Boeckx, 2010; Boeckx and Benítez-Burraco, 2014a). The core combinatorial operation in natural language is usually called "Merge" (Chomsky, 1995). As pointed out by Boeckx and Benítez-Burraco (2014a: 5), merge allows for "the compositional, freely combining, systematic, cross-modular semantics that is manifest in all human languages".

The retrieval of archaic human genetic materials (Green et al., 2010; McLean et al., 2011; Meyer et al., 2012; Gokhman et al., 2014; Prüfer et al., 2014; Pääbo, 2014) has uncovered genetic and epigenetic changes that may have contributed to the emergence of our species-specific mode of cognition, including our linguistic abilities (see Boeckx and Benítez-Burraco, 2014a,b; Benítez-Burraco and Boeckx, 2015). However, other changes plausibly contributed to this emergence. Recent research has shown in particular that RNA regulation of epigenetic processes, RNA editing, and the controlled mobilization of transposable elements may explain crucial aspects of the evolution of the human brain and of human cognition (Barry and Mattick, 2012).

Piattelli-Palmarini and Uriagereka (2004: p. 341) suggested that an evolutionary understanding of our NS should "link that kind of syntax with the workings of very

elementary levels of biological organization, such as the structure of the adaptive immune system and its biochemical base". According to them, "the evolution of an entire mechanism (such as NS) which establishes one or more interfaces is most likely epigenetic in nature, and viral interactions, generally understood, provide the right level of complexity" (p. 359). Appealing to viral infection built on four facts: (i) viral infection may resemble epigenetic modifications of the DNA (in contrast, gene changes are usually either too specific or too general); (ii) viral infections are commonly tissue-specific (while gene mutations are usually pleiotropic); (iii) viruses can infect an entire population (whereas gene mutations spread slowly), thus providing an approach to how language may be inherited by a group, not just an individual; and (iv) lastly, viruses can integrate into a host genome (consequently, modifications brought about by the viral DNA itself or by the integration event can be subsequently inherited by the offspring).

We will revisit this hypothesis in light of findings affecting three factors: (i) there is an intimate crosstalk between the immune system and the brain (Ziemssen and Kern, 2007; Kokaia et al., 2012; Ransohoff and Brown, 2012); (ii) horizontal gene transfer (HGT), including viral transfer, occurs in metazoans on a previously unsuspected scale (Crisp et al., 2015); this represents a form of genetic variation that affects the evolution of species (Koonin and Wolf, 2012; Syvanen, 2012; Baltrus, 2013); and (iii) the tight association between the human body and its microbiota may affect brain development, function, and evolution. We expect these factors to have reshaped the primate brain responsible for modern cognition, contributing to the emergence of language.

Recent research has shown how bacterial colonization of the gut is central to postnatal development of systems that influence brain programming and signaling, particularly the immune system (Borre et al., 2014). For example, the developing serotonergic system responds differentially to diverse microbial colonization patterns because the gut microbiota reduce the amount of tryptophan available for serotonin synthesis (O'Mahony et al., 2015). While the involved enzymes are immune-responsive (O'Mahony et al., 2015), serotonin contributes to innate and adaptive responses of the immune system (Baganz and Blakely, 2013). Interestingly, differences in serotonin levels are a hallmark of cognitive disorders involving language deficits, like autism (Abramson et al., 1989; Hranilovic et al., 2007). Neuropsychiatric disorders may also result from the distortion of serotonin/immune conversations (Baganz and Blakely, 2013). Microbes colonizing the gut produce other neuroactive compounds, including GABA and dopamine (Wall et al., 2014), as well as molecules with neuromodulatory potential, like short chain fatty acids (Stilling et al., 2014a). Moreover, Fitzpatrick (2014) and Stilling et al. (2014a) have argued that (symbiont) microbes are epigenetic effectors, as they share most of the features of classical epigenetic mechanisms. Finally, Stilling et al. (2014b) have suggested that epigenetic mechanisms mediate host-microbe communication, resulting in changes in brain adaptation and plasticity.

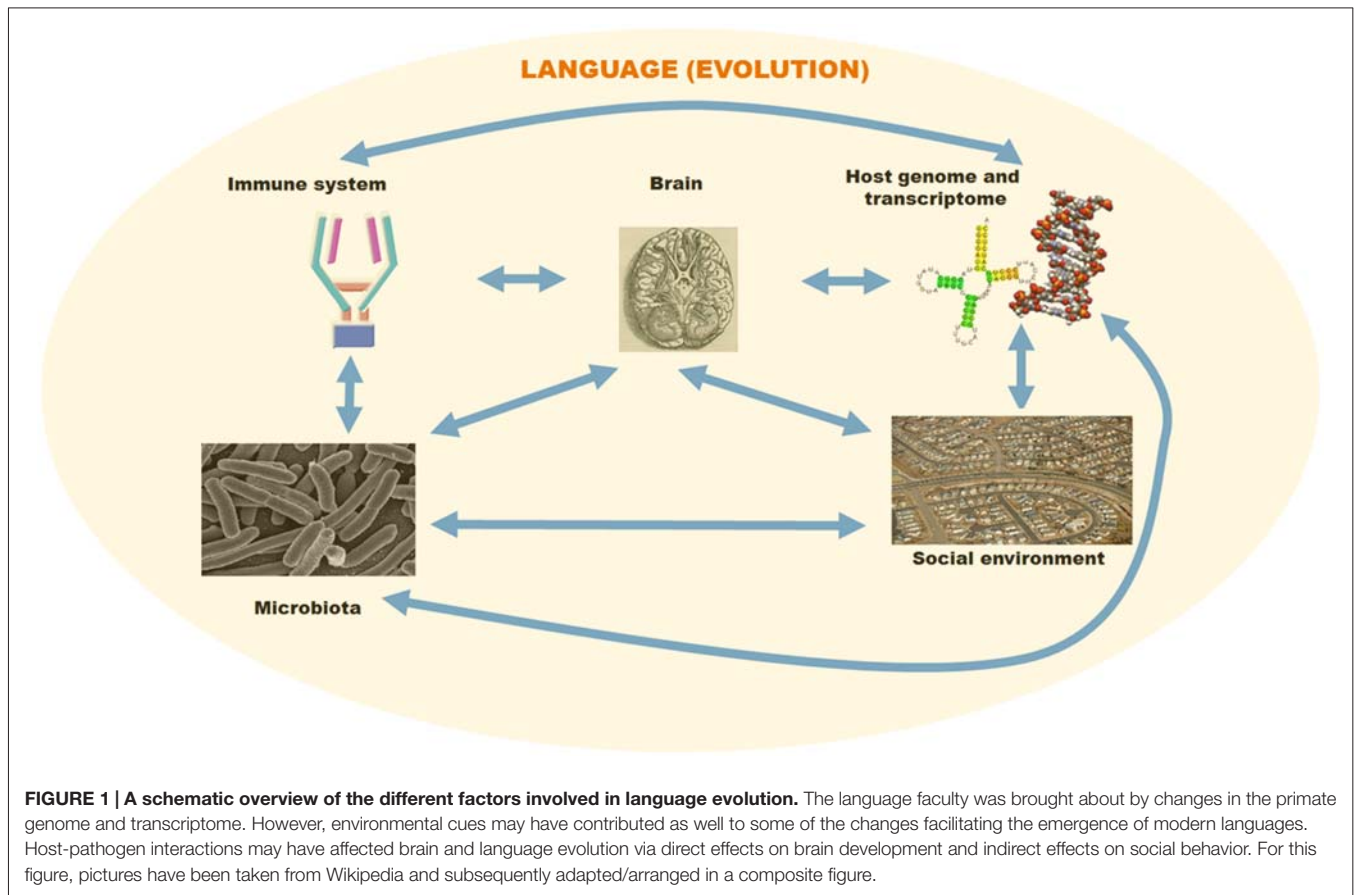Properties that are latent and emerge in response to a change in the environment may be relevant to the evolution of language, in view of evidence of social transmission and cultural evolution in language variation and the acquisition of grammatical properties (Boeckx, 2013; Benítez-Burraco et al., under review). While changes in the interactomes of language-related genes are a condition for "cognitive modernity", as such they do not entail immediate "behavioral modernity". For that, the environment arguably had to be of the right kind, exhibiting a "cultural niche" encompassing the social, behavioral, and neural conditions of human culture (see Tomasello, 2009, 2014). In a nutshell, human microbiota may be one of these conditions (**Figure 1**).

Obviously, we are not claiming that "a language virus" exists, or that human-specific bacterial symbionts may account for human-specific cognitive traits. What we hypothesize, instead, is that these mechanisms (e.g., a modification in our feeding habits that could have brought about a subtle change in our ancestral microbiota) may have affected brain development in some crucial sense. The complex language faculty that anatomically-modern humans (AMHs) present appears to have resulted from different kinds of changes, from mutations in key genes to alterations in the transcriptional profile of others. We expect our hypothesis to be just one piece of a large puzzle.

In section "Immune(-like) Mechanisms and language Evolution," we discuss the convergent (co)-evolution of the brain and the immune system. We focus on the similar mechanisms that seem to account for the molecular diversity observed in both domains, but also on the crosstalk between the immune system and the brain. We then move to the realm of pathogens. In sections "Viral Vectors and Language Evolution" and "Non-Viral Vectors and Language Evolution," we examine several genes that may have been horizontally transferred to the human genome and are expected to interact with genes that we regard as important for language evolution. In section "Microbiota and Language Evolution," we discuss the broader effect of the microbiota on brain development and function and introduce the idea of the *language hologenome*. Finally, in section "From Brain Rewiring to Language Evolution," we speculate on how these findings could help us improve our current understanding of the linguistic mind and its evolution.

IMMUNE(-LIKE) MECHANISMS AND LANGUAGE EVOLUTION

The idea that immune-related mechanisms may have contributed to the brain rewiring underlying modern syntax boils down to two facts. First, brain functions result in part from neurons assembled during development into an exponentially greater number of networks. This depends on the expression of molecular cues onto the cell surface of the neurons-to-be-assembled: tens of thousands of neuronal networks are characterized by distinctive molecular codes. Changes in brain wiring and function should be expected from changes in neural interconnection patterns relying of this complex code. The mechanisms that allow this diversity are similar to those regulating the tuning of cell receptor interactions in the immune system. Second, the immune

FIGURE 1 | A schematic overview of the different factors involved in language evolution. The language faculty was brought about by changes in the primate genome and transcriptome. However, environmental cues may have contributed as well to some of the changes facilitating the emergence of modern languages. Host-pathogen interactions may have affected brain and language evolution via direct effects on brain development and indirect effects on social behavior. For this figure, pictures have been taken from Wikipedia and subsequently adapted/arranged in a composite figure.
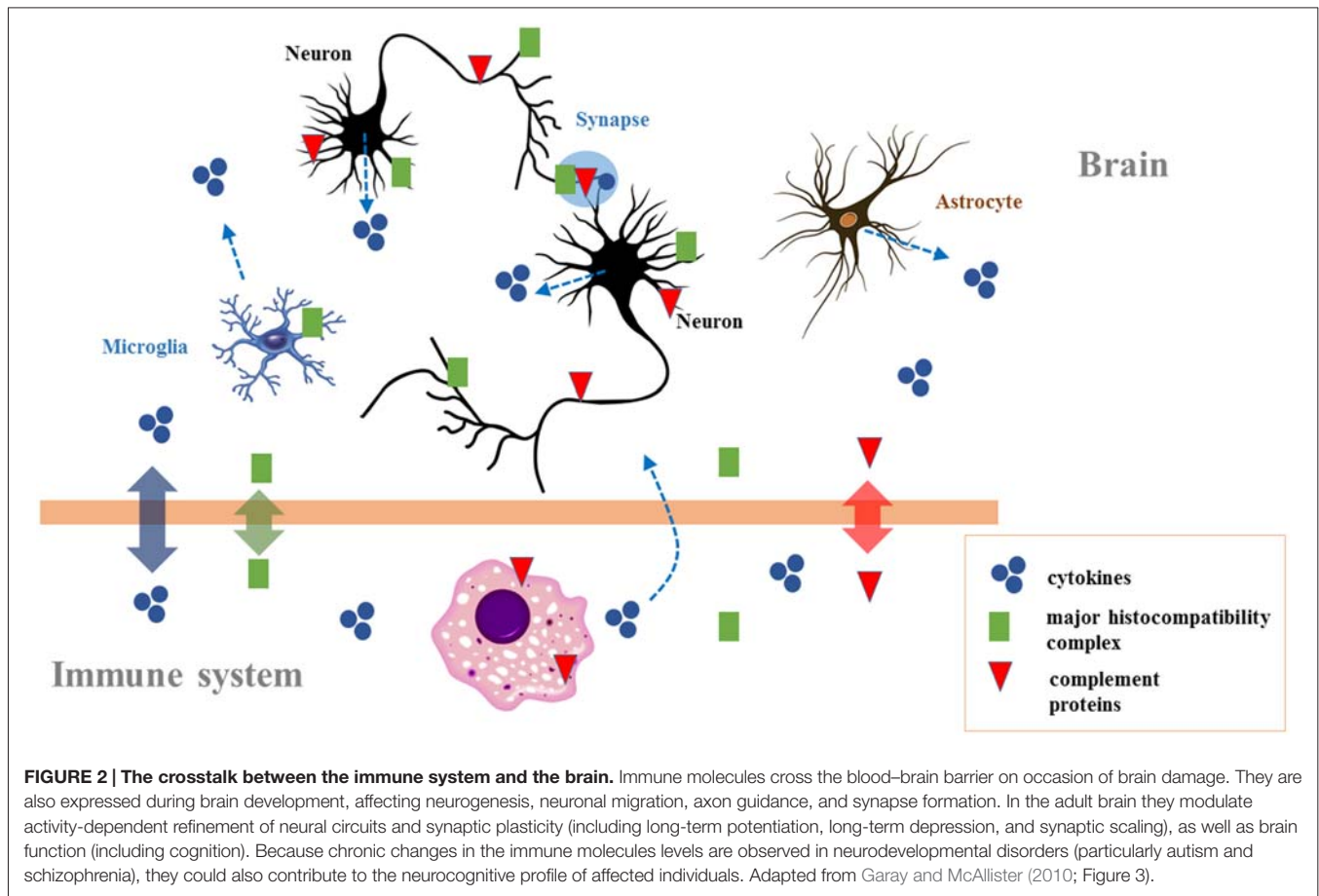
system directly affects brain development. Consequently, we should expect changes in brain wiring and function from changes in immune response (for example, after pathogen infection).

Both parallelisms are worth exploring vis-à-vis language evolution (**Figures 1**, **2**). Interestingly, brain and immune complexity appear to have evolved in parallel. Insects have minimal brains and no adaptive immunity, reptiles have larger brains and a basic adaptive immunity, mammals have the largest brains and full adaptive immune systems. Both systems may have evolved in a convergent fashion, if the requirements for complex intercellular communication networks ended up selecting for similarly structured networks in the immune system and our brains. Then again, actual co-evolution between the immune system and the brain may have taken place instead. We would like to highlight two aspects of these broad parallelisms.

First, many neuronal cell surface receptors involved in neuronal interactions contain immunoglobulin domains. These molecules regulate neuronal migration and survival, axon guidance, and synaptic targeting during development (Maness and Schachner, 2007). Among those in the immunoglobulin superfamily that are relevant to language one finds the ROBO/SLITs signaling proteins (see Boeckx and Benítez-Burraco, 2014b). Another interesting example is NCAM, which

interacts with VCAM1, a protein bearing a fixed change (D414G) in AMHs as compared to Neanderthals/Denisovans (Pääbo, 2014, Table S1). NCAM plays a role in axonal/dendritic growth and synaptic plasticity, and ultimately the development of cognitive abilities (Prag et al., 2002; Hansen et al., 2008). Aberrant expression patterns of *NCAM* or incorrect posttranslational modifications of the protein have been linked to cognitive disorders involving schizophrenia-like symptoms (Vawter et al., 2001; Atz et al., 2007). The gene is a target of RUNX2 (Kuhlwilm et al., 2013) and FOXP2 (Spiteri et al., 2007), both crucial factors involved in language development (Boeckx and Benítez-Burraco, 2014a,b).

Before reviewing another aspect of the parallelisms, note that other surface molecules involved in cell-recognition/adhesion in brain development/functioning are often endowed with immunoglobulin-like properties. We expect common molecular mechanisms explaining diversity in immunoglobulins and neuronal adhesion molecules. For example, the functional heterogeneity of these surface molecules amounts to the independent stochastic expression of given genes' autosomal alleles. One instance is *DSCAM*, a candidate for Down syndrome defects involved in neural wiring and innate immunity (Schmucker and Chen, 2009). Another, clustered protocadherins (Pcdhs), which are arranged in clusters and expressed by alternative promoter choice. Pcdh isoforms

FIGURE 2 | The crosstalk between the immune system and the brain. Immune molecules cross the blood–brain barrier on occasion of brain damage. They are also expressed during brain development, affecting neurogenesis, neuronal migration, axon guidance, and synapse formation. In the adult brain they modulate activity-dependent refinement of neural circuits and synaptic plasticity (including long-term potentiation, long-term depression, and synaptic scaling), as well as brain function (including cognition). Because chronic changes in the immune molecules levels are observed in neurodevelopmental disorders (particularly autism and schizophrenia), they could also contribute to the neurocognitive profile of affected individuals. Adapted from Garay and McAllister (2010; Figure 3).

are further arranged in heteromultimers that represent selective binding units for cell-cell interactions (Yagi, 2012, 2013; Sotomayor et al., 2014). Overall, clustered Pcdhs play critical roles in axonal projection, synaptic formation, dendritic arborization, and neuronal survival (Chen and Maniatis, 2013; Hirayama and Yagi, 2013). Some of these have been related to neurological diseases and cognitive disorders involving language deficits (for review, see Hirabayashi and Yagi, 2014). Thus *PCDH10* has been linked to autism (Tsai et al., 2012), while mutations in *PCDH19* cause epilepsy and mental retardation (Dibbens et al., 2008). More to our point, Williams et al. (2006), Chance and Crow (2007), or Crow (2008) argue that different chromosomal reorganizations/mutations affecting *PCDH11* triggered a modification of the brain lateralization pattern that contributed to language emergence. Finally, the editing enzymes may also explain diversity in immunoglobulin and neuronal adhesion molecules, which could affect language evolution (see Dong et al., 2012 on the downregulation of *APOBEC3A* and *APOBEC3C* in the inferior parietal lobule of psychotics; for LINE-1 and Alu elements, immobilized by these enzymes, as linked to cognitive disorders, see Muotri et al., 2010; Hancks and Kazazian, 2012; Thomas et al., 2012).

As a second aspect of crosstalk between the immune system and the brain (and, for us, the parallelism between immunity and syntax), note that immunoglobulin cell surface receptors are also active in the brain (**Figure 2**). They play a role in the development of different cell types (Nakahara et al., 2003) and contribute to the functional establishment in different brain areas (Andoh and Kuraishi, 2004; Nakamura et al., 2007). Moreover, their aberrant activation contributes to the pathogenesis of neurodegenerative conditions (Okun et al., 2010). For example, in amyotrophic lateral sclerosis immunoglobulin G (IgG) uptake by motor neurons affects transmitter release from motor axon terminals (Mohamed et al., 2002). More generally, most of the molecules whose production is triggered upon infection play a role in the normal development of the brain. Thus cytokines modulate neurogenesis in response to an activated immune system and seem involved in neurobiological mechanisms associated with cognitive processes (Borsini et al., 2015; **Figure 2**). At the same time, the altered homeostasis of cytokines impacts brain development and predisposes to mental diseases (Ratnayake et al., 2013). Ge et al. (2014) link cytokine levels, functional polymorphisms of immunity-related proteins, and language impairment. Similarly, the *complement*, a component of the defense cascade of innate immunity comprising fluid-phase and

cell-associated proteins (Wagner and Frank, 2010), also plays a role in brain wiring and function (**Figure 2**). This "complement activation" contributes to the remodeling of synaptic circuits during early stages of brain development (Eggleton et al., 2000; Bialas and Stevens, 2013), but it is necessary as well for brain wiring after birth, a failure in which may result in autism or schizophrenia (Patterson, 2011). Overall, normal brain-immune communication is crucial for the development of the brain, while alterations in brain-immune communication (e.g., caused by pathogen infections) give rise to neuropsychiatric disorders. This is, in short, why we expect changes in brain-immune crosstalk to have contributed to brain rewiring during recent hominin evolution.

Since the logic of the "immune syntax" hypothesis was "based on properties of immune responses to viral intruders" (Piattelli-Palmarini and Uriagereka, 2004: p. 366), we next explore the putative effects of pathogenic infections on language evolution. Again, infections can affect a population, thus contributing to spread innovations, and because microbes can integrate into the host genome, modifications brought about by their genetic material or the integration event can be inherited by the offspring.

VIRAL VECTORS AND LANGUAGE EVOLUTION

Chronic and neuropathic viral infections produce loss of neurons and axons that result in neurodegenerative and neurocognitive diseases (Karim et al., 2014). Viral infection has been hypothesized to (subtly) contribute, also, to cognitive developmental disorders. According to Fruntes and Limosin (2008), prenatal exposure to viruses may cause early brain damage and an aberrant pattern of neuronal migration and expression of neural cell adhesion molecules that may result in schizophrenia. Some viral infections can give rise to loss of language (Marques et al., 2014). Viruses are hypothesized to cause this effect by direct brain lesion, by triggering an autoimmune response during development, or by inducing the maternal immune activation during growth (Garbett et al., 2012). Interestingly, viruses that specifically attack the immune system can produce cognitive impairment too, as commonly observed in HIV-infected patients (Rosca et al., 2012). Viral infection can also affect the cellular mechanisms involved in somatic variation and neuronal diversity within the brain (with deleterious consequences). For instance, changes in the splicing profile of *MOR* induced by the HIV-1 virus sometimes result in neurocognitive impairment (Dever et al., 2012).

Importantly, viruses are also able to transfer DNA or RNA fragments to the host species that may be permanently integrated in their genomes and be subsequently transmitted to offspring (Liu et al., 2011). The human genome expresses multiple genes acquired from or potentially transferred by viruses (Crisp et al., 2015). A literature search [via PubMed and OMIM (http://www.ncbi.nlm.nih.gov/omim/)] helped us determine whether, and if so to what extent, some of these genes may have contributed to the changes that we believe important

for language evolution (reviewed in Boeckx and Benítez-Burraco, 2014a,b; Benítez-Burraco and Boeckx, 2015). We have relied as well on computer tools [mostly on String 10 (http://string-db.org/)] to learn about the robustness of the links we posit. As for phylogenetic changes, we have relied on available data on genetic and epigenetic changes that occurred after our split from Neanderthals and Denisovans.

We have found that several of the genes potentially transferred from viruses are candidates for cognitive disorders entailing language deficits, or play a role in aspects of brain development and function that we believe relevant for language processing, or interact with some of our candidates for language evolution (**Table 1**; **Figure 3**). Among them, we have found genes that are upregulated upon RUNX2 transfection [*SERPINE1, ELOVL4, CXCR4, CCR7, GPX2, GPR1,* and *DHFR* (Kuhlwilm et al., 2013)], and several targets of *FOXP2* [*FGR, CLEC2D, CCRL2, CXCR4,* and *GPR1* (Spiteri et al., 2007)]. *RUNX2* is our core candidate underlying the changes that prompted the globularization of the human brain, whereas *FOXP2* is a renowned gene involved in vocal learning (Graham and Fisher, 2013). The evolutionary modification of the interactomes of both genes may have contributed to the emergence of our language-readiness and refined the devices involved in the externalization of language (for details, see Boeckx and Benítez-Burraco, 2014a,b; Benítez-Burraco and Boeckx, 2015).

If language evolution was affected by changes in the immune system/brain crosstalk, it is interesting that *GPR1* turns out to be among the genes potentially transferred to humans from viruses. This gene is expressed in the hippocampus of primates only (as compared to rodents) and encodes an orphan G protein-coupled receptor (Marchese et al., 1994). GPR1 functions as a co-receptor for some viruses, making the cell more susceptible to infection (Shimizu et al., 1999). This makes us wonder whether posterior infections or infection-related events affected the evolution of cognition in primates only, as compared to other mammals. We also find it interesting that many genes that were putatively transferred from viruses would encode cytokine- and chemokine-related proteins. Again, such immune-signaling molecules and their functional partners do not only mediate viral infection: they are also expressed in the brain, in whose development and function they play a role, in synaptic pruning (Paolicelli et al., 2011), brain disease (Moretti et al., 2015), and memory and learning (Williamson and Bilbo, 2013); see e.g., van der Meer et al. (2000) on *CCR2* and *CXCR4*, two of the genes in Crisp et al.'s (2015) list. It should be established whether any of these genes played a role in the evolution of the memory and learning capacities presupposed in the faculty of language.

Other transferred genes (present in primates only) are endogenous retroviruses (HERVs). These are non-coding DNA remnants of retroviral infections occurred during primate evolution (Antony et al., 2004). While HERV activity pertains to individual genomic variation associated to chromosomal rearrangements (Weckselblatt and Rudd, 2015), it may also account for evolutionary differences across species, as accumulation of retroelements parallels the increment of evolutionary complexity of the host species (Kidwell, 2002).

TABLE 1 | Genes discussed in sections 3 and 4.

Core candidate genes for language evolution	Top-25 GO biological processes of core candidates genes for language evolution	Viral genes important for language evolution	Non-viral genes important for language evolution
ABL1	Nervous system development	CCR2	AHNAK
AKT1	Neurogenesis	CCR7	AHNAK2
APOE	Generation of neurons	CCRL2	AL158821.1
ARX	Organ development	CLEC2D	AL356585.1
ASCL1	System development	CXCR4	AP4E1
AUTS2	Central nervous system development	DHFR	ASTN2
BMP2	Multicellular organismal development	EBLN2	CARNS1
BMP7	Anatomical structure morphogenesis	ELOVL4	CDKL5
CBL	Regulation of developmental process	ERVFRD-1	CENPF
CDC42	Cellular developmental process	ERVW-1	CYP26A1
CEBPB	Anatomical structure development	FGR	CYP26C1
CITED2	Cell differentiation	GPR1	DAZ2
CMIP	Regulation of multicellular organismal development	GPX1	FAM230A
CNTNAP2	Single-organism developmental process	GPX2	FLJ22447
CREBBP	Developmental process	SERPINE1	GIMAP8
CTNNB1	Head development	SRC	GOLGB1
DISP1	Cell development	XCR1	HAS1
DLL1	Neuron differentiation	YES1	HAS3
DLX1	Brain development		IL4I1
DLX2	Regulation of multicellular organismal process		IRG1
DLX5	Tissue development		LMO7
DLX6	Forebrain development		MAP6
DYRK1A	Regulation of cell differentiation		MSRA
EGR1	Regulation of cell development		MT-ND4L
EP300	Regulation of gland development		MYO10
ERBB4			NQO1
FEZF2			PADI2
FMR1			PADI3
FOXG1			PLAU
FOXO1			RAD21-AS1
FOXP1			RIMKLA
FOXP2			RTL1
FOXP2			SERPINB2
GAD1			
GBX2			
GLI3			
GTF2I			
HES1			
LHX2			
MAPK1			
MECP2			
MEF2A			
NCAM1			
NCOA6			
NFASC			
NKX2–1			
NODAL			
NRG1			
OTX2			
PAX6			
POU3F2			
PTEN			
ROBO1			
ROBO2			
RUNX2			
SATB2			
SHH			
SIRT1			

(Continued)

TABLE 1 | (Continued).

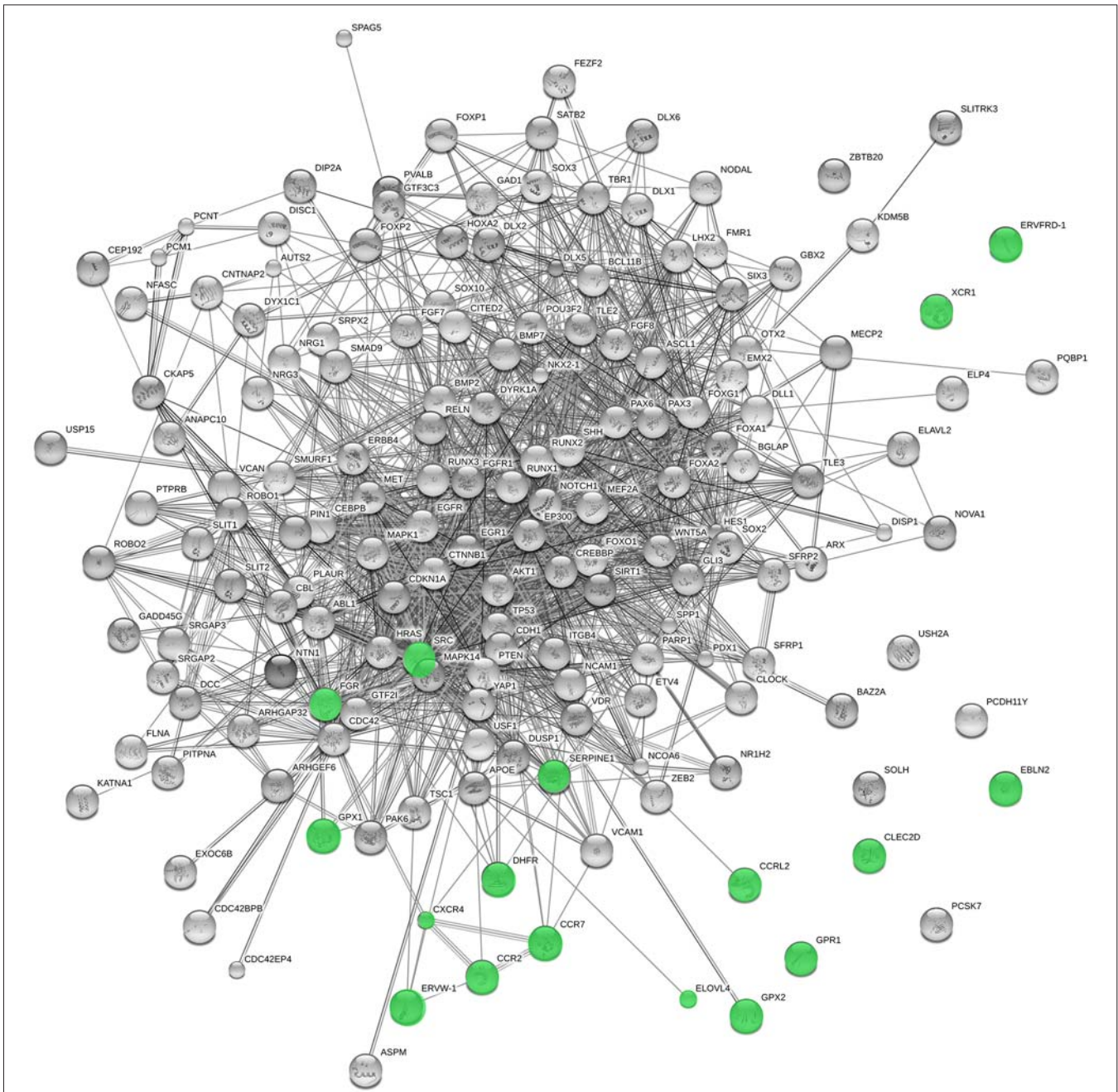| Core candidate genes for language evolution	Top-25 GO biological processes of core candidates genes for language evolution	Viral genes important for language evolution	Non-viral genes important for language evolution
SLIT1			
SLIT2			
SOLH			
SPAG5			
SRGAP2			
SRGAP3			
SRPX2			
TBR1			
TP53			
TSC1			
VCAM1			
ZBTB20			

The first column contains core candidates for the evolution of language as posited by Boeckx and Benítez-Burraco (2014a,b) and Benítez-Burraco and Boeckx (2015). The second provides a GO classification of these genes according to Panther (http://pantherdb.org); only the top-25 functions after a Bonferroni correction have been included. The last two columns include the horizontally-transferred genes from viruses and non-viral organisms, respectively, highlighted here as potential new candidates for language evolution.

In all vertebrates, there is evidence of transposable element-mediated genomic rearrangements potentially associated with or subsequent to speciation events, which suggests that these are drivers of genomic and biological diversity in vertebrates (Böhne et al., 2008). Interestingly, HERVs travel in waves of infection and subsequently transition from exogenous to endogenous forms (Ishida et al., 2015). Curiously, the emergence of HERVs coincided with that of adaptive immunity (Litman et al., 2010). Although the vast majority of retroviruses have been inactivated, some are still expressed in different tissues (Seifarth et al., 2005; Yi et al., 2006), playing regulatory functions and more (Bannert and Kurth, 2006). Activation or upregulation of HERVs have been linked to AMH-specific neurocognitive conditions like autism (Balestrieri et al., 2012) or schizophrenia (Frank et al., 2005), which helps us illustrate how HERVs may have affected genes involved in language evolution.

According to Suntsova et al. (2013) HERVs may serve as tissue-specific enhancers for brain-related genes involved in schizophrenia—specifically *PRODH*, which codes for a proline dehydrogenase enzyme that plays a role in neuromediator synthesis in the brain. The mechanism involves the transcription factor SOX2, regulated by RUNX2 (Yoon et al., 2014). At the same time, SOX2 regulates *PQ15P1*, a gene linked to developmental delay, intellectual disability and microcephaly (Li et al., 2013), which interacts with POU3F2 (Li et al., 2013). Intron 8 of *FOXP2* contains an AMH-specific substitution that affects a binding site for POU3F2 (Maricic et al., 2013). Moreover, schizophrenia has been claimed to result from epigenetic changes that deregulate HERV-activity (Diem et al., 2012). Importantly, among the environmental factors causing these epigenetic changes one finds viral infections, which can deregulate the epigenetic control naturally involved in silencing HERVs via the transactivation of endogenous retroviruses (Perron and Lang, 2010). We believe it is worth exploring whether any of these effects played a role in language evolution.

Among the genes that may have been transferred to primates we found *XCR1*, which encodes a chemokine receptor belonging to the G protein-coupled receptor superfamily (Heiber et al., 1995) and is a FOXP2 target (Vernes et al., 2011). Additionally, *ERVW-1* and *ERVFRD-1* are found in all primates except tarsiers. *ERVW-1* encodes syncytin 1, a membrane protein that contributes towards immune tolerance and is found upregulated in astrocytes and glial cells of individuals with multiple sclerosis (Antony et al., 2004). *ERVFRD-1* encodes syncytin 2, a membrane protein with inmunosuppresive activity (Blaise et al., 2003). Similarly, *EBLN2* (found only in macaques, gibbons, and the great apes) encodes a protein akin to the Borna disease viruses (Horie et al., 2010). One gene was transferred to our genome after our split from the great apes; namely, *AP001468.1*. Unfortunately, it encodes a protein of unknown function.

To be clear: we are not claiming that all those genes were transferred to (and spread among) modern humans by a viral vector and that these events allowed modern language to emerge and spread so quickly. Most of the genes highlighted were transferred *before* the split of great apes from other mammals. However, because some of these are functionally related to genes that show differences when comparing AMHs to Neanderthals and/or Denisovans, we shouldn't discard differences between hominin species regarding the functions these genes contribute to. Such may be the case of *SRC*, for instance, which is functionally related to *VCAN*: the specific blockade of Src activity abolishes versican-1-induced differentiation of PC12 cells into neurons (Wu et al., 2004). Versican-1 is involved in neurite outgrowth of hippocampal neurons (Xiang et al., 2006) and shows a fixed N3042D change in AMHs (Pääbo, 2014; Table S1). Similarly, two human-specific conserved deletions (hCONDELs; although shared with Neanderthals) exist upstream *YES1* and downstream *GPX1*, respectively (McLean et al., 2011)—which are two of the genes highlighted by Crisp et al. (2015).

FIGURE 3 | Functional links predicted by String 10 among candidates for the evolution of language (nodes in gray) and the horizontally-transferred genes from viruses highlighted here as potential new candidates (nodes in green). Stronger associations between proteins are represented by thicker lines. The medium confidence value was 0.0400 [a 40% probability that a predicted link exists between two enzymes in the same metabolic map in the KEGG database (http://www.genome.jp/kegg/pathway.html)]. String 10 predicts associations between proteins that derive from a limited set of databases: genomic context, high-throughput experiments, conserved coexpression, and the knowledge previously gained from text mining (Szklarczyk et al., 2015). This is why the figure does not represent a fully connected graph (evidence for additional links are provided in the main text). Importantly, the diagram only represents the potential connectivity between the involved proteins, which has to be mapped onto particular biochemical networks, signaling pathways, cellular properties, aspects of neuronal function, or cell-types of interest that can be confidently related to aspects of language development and function (see **Table 1**).

Most changes implicated in language evolution are expected to have impacted the transcriptome. Regulatory switching due to the horizontal transfer of regulatory regions have been attested in bacteria (Nijveen et al., 2012; Oren et al., 2014). It may be transposable elements that harbor these regulatory elements, allowing them to move across strains (Siddique et al., 2011).

Also, the consequences for gene regulation of the viral infections occurred during our recent history are worth mentioning. For example, HERVs are endowed with transcriptional activity enabling them to function as alternative promoters or enhancers, ultimately to modify the expression of neighboring genes (Le Dantec et al., 2015). Additionally, viral infections can modify the brain epigenetic landscape, as HERVs illustrate. Thus, we should expect the impact of viral infections on brain function and evolution to go beyond the roles reviewed above.

Most epigenetic changes brought about by viruses affect the expression of host immune genes, to render the immune responses inactive to their antigens (Adhya and Basu, 2010). However, viral infection *per se* may induce changes in the brain epigenetic landscape even in the latent phase. For example, latent HIV-1 is associated with increased levels of BCL11B, a chromatin modifier encoded by one the genes regulated by RUNX2, which may result in abnormal transcriptomes (Kuhlwilm et al., 2013). Exogenous factors exacerbate the impact of viral infections on epigenetic modification of the brain (Desplats et al., 2013). For instance, HIV-1 infection in conjunction with drug abuse brings about changes in the expression of *DNMT1* (a key enzyme responsible for DNA methylation), which result in differential methylation on genes related to neurodegeneration and dopamine metabolism in the frontostriatal circuits. Drugs too can cause epigenetic changes at the viral promoter, resulting in altered gene expression (Shirazi et al., 2013). One has to wonder whether such mechanisms contributed to changes required for the emergence of language-readiness.
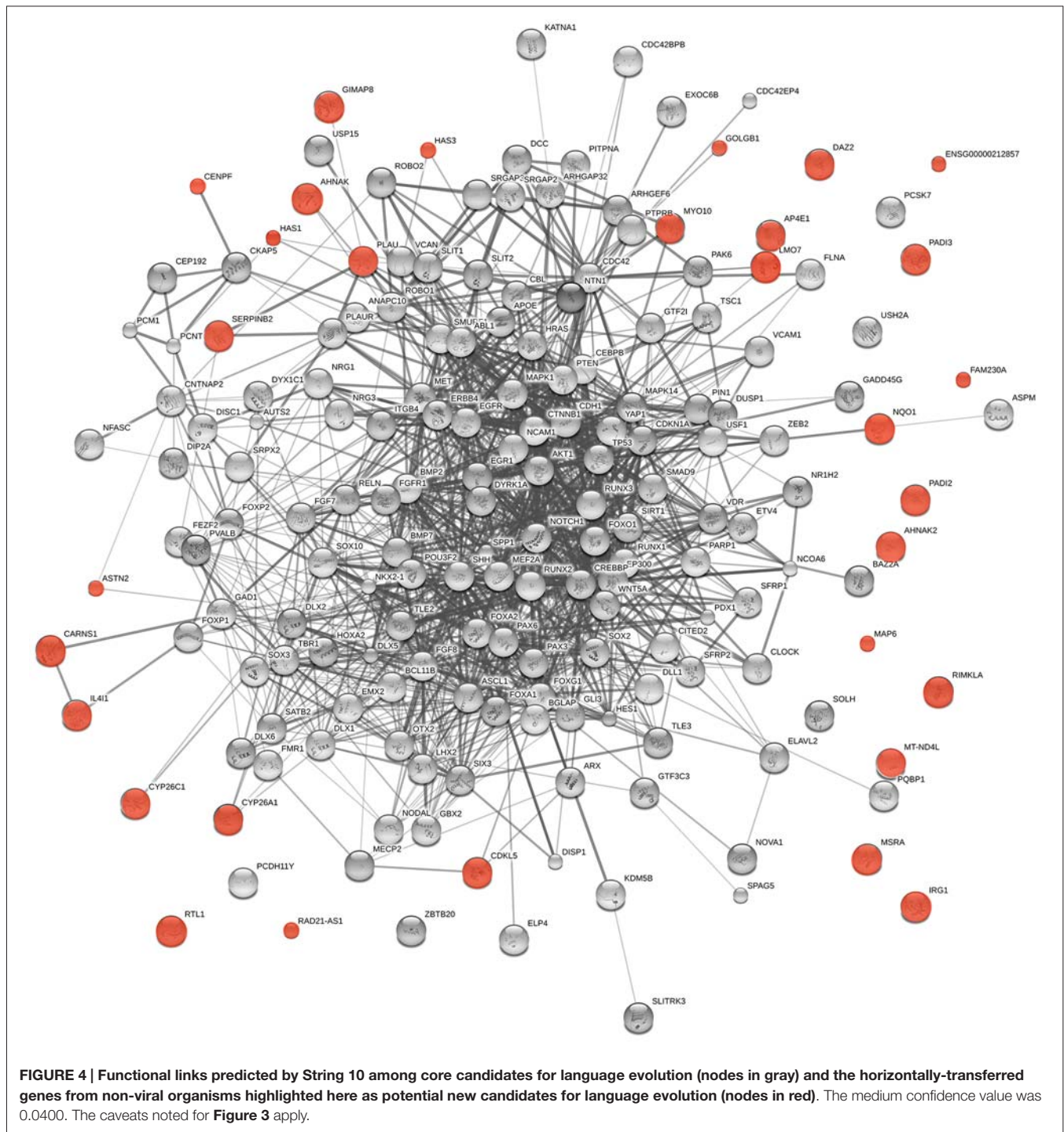
NON-VIRAL VECTORS AND LANGUAGE EVOLUTION

The logic of Piattelli-Palmarini and Uriagereka's hypothesis applies to *any infectious vector* that may transfer genetic material. There is growing evidence suggesting that the microbiota impact brain development and function and, ultimately, cognition and behavior (Cryan and Dinan, 2012 and see "Introduction" Section). Nearly 150 genes from other organisms are expressed in human cells (Crisp et al., 2015). Following the *modus operandi* described in section "Viral Vectors and Language Evolution," we have found among them language-related genes, including targets of RUNX2 (*CENPF*, *SERPINB2*, *IL4I1*, *AHNAK*, *GOLGB1*, *NQO1*, *AHNAK2*, *RTL1*, and *LMO7*) and FOXP2 (*HAS1* and *PLAU*) (Spiteri et al., 2007; **Figure 4**).

Other genes are functionally related to genes in the interactomes that we believe important for language evolution (**Figure 4**) or give rise to language or cognitive disorders entailing aberrant modes of thinking when mutated. Thus, *MAP6* encodes a protein that binds to and stabilizes microtubules and has been related to schizophrenia (Shimizu et al., 2006). In mice, deletion of *Map6* gives rise to synaptic defects and brain dysfunctions, ultimately to cognitive deficits similar to those observed in schizophrenics (Volle et al., 2013). *CDKL5* has been related to Rett-like syndrome and X-linked West syndrome, two cognitive disorders entailing language deficits (Kalscheuer et al., 2003; Tao et al., 2004; Scala et al., 2005). Mutations or deletions in *AP4E1* cause a syndrome involving

microcephaly, facial dysmorphisms, cognitive impairment and speech delay (Abou Jamra et al., 2011; Moreno-De-Luca et al., 2011). *MYO10* controls the direction and morphogenesis of cells during radial cortical neuronal migration (Ju et al., 2014). Also of interest are two isoforms of the hyaluronan synthase, encoded by *HAS1* and *HAS3*. *HAS1* is upregulated in astrocytes during normal brain aging (Cargill et al., 2012), whereas *Has3*(–/–) mice exhibit altered neuronal activity and seizures (Arranz et al., 2014). Lastly, *ASTN2* regulates the levels of ASTN1, a neuron-glial ligand important for glial-guided neuronal migration, a key step in the development of laminar architecture of cortical regions of the mammalian brain (Wilson et al., 2010). Mutations in *ASTN2* have been related to neurodevelopmental disorders, including autism spectrum disorder and speech delay (Lionel et al., 2014), and to Alzheimer's disease (AD; Wang et al., 2015a).

Several of the genes transferred from non-viral organisms are involved in the metabolism of retinoic acid in the brain. Retinoic acid controls brain changes relevant to language development, in connection with *FOXP2* (for review, see Benítez-Burraco and Boeckx, 2014), which potentiates retinoic acid induction of genes involved in neural differentiation (Devanna et al., 2014). Two of the three all-trans retinoic acid—degrading cytochromes, *CYP26A1* and *CYP26C1*, remove retinoic acid in the forebrain to ensure proper head development (Ribes et al., 2007; Uehara et al., 2007). Both genes are also involved in the regulation of retinoid signaling across multiple connected song nuclei and auditory brain regions in songbirds, modulating the circuitry that underlies the acquisition and production of learned vocalizations (Roeske et al., 2014). Another gene worth highlighting is *MSRA*, which is regulated by retinoic acid (Pascual et al., 2009) and regulates COMT activity (hence dopamine levels) in the brain (*COMT* is a strong candidate for several cognitive disorders, including schizophrenia; Moskovitz et al., 2014). Finally, among the genes transferred from bacteria we have found *IRG1*. This is an interferon-stimulated gene regulated by microRNA that reduces the susceptibility of neurons from specific areas of the brain to viral infection (Cho et al., 2013).

Although these genes were transferred between the common ancestors of Chordata and the primates, they are functionally related to genes involved in language evolution (**Figure 4**), some of which have changed after our split from Neanderthals and Denisovans. However, a handful were transferred later. Found in primates only, except tarsiers, *FAM230A* contains a site of frequent translocations and micro-deletions in DiGeorge syndrome (Kurahashi et al., 2007), a complex disease involving language deficits (Swillen et al., 1999; Glaser et al., 2002). *MT-ND4L* is found in great apes only and encodes the subunit 4L of the mitochondrial NADH dehydrogenase. Two genes of unknown function (*AL356585.1* and *AL158821.1*) are shared by gorillas, chimpanzees and humans, whereas two are found in chimpanzees and humans only: *DAZ2*, a member of the DAZ gene family involved in spermatogenesis, and *RAD21-AS1*, which encodes a ncRNA (*RAD21*), is highly expressed in human fetal cerebral cortex, and is thought to play a key role in brain development (Pemberton et al., 2007).

FIGURE 4 | Functional links predicted by String 10 among core candidates for language evolution (nodes in gray) and the horizontally-transferred genes from non-viral organisms highlighted here as potential new candidates for language evolution (nodes in red). The medium confidence value was 0.0400. The caveats noted for **Figure 3** apply.

Finally, *FLJ22447* was transferred to humans only, although before the split from Neanderthals/Denisovans (Gokhman et al., 2014, Table S2). This gene encodes an ncRNA that interacts with *FUS*, an RNA/DNA binding protein involved in transcription, DNA repair, and RNA splicing, which has been related to frontotemporal dementia (Wang et al., 2015b).

Some of the genes transferred from other organisms may be differentially regulated in AMHs, as compared to other close hominins, resulting from several factors. First, from human-specific deletions, like the one affecting the region upstream *PADI3* (McLean et al., 2011). Second, from differences in methylation patterns, like those expected for *MSRA*, involved in COMT action (Moskovitz et al., 2014); *PADI2*, involved in

the catabolism of myelin basic protein (Asaga et al., 2002); *GIMAP8*, linked to AD (Ishigami et al., 2005) and multiple sclerosis (Mastronardi et al., 2007); *CARNS1*, which catalyzes the biosynthesis of homocarnosine (Drozak et al., 2010); and *FLJ22447* (Gokhman et al., 2014, Table S2). Third, differential regulation may result from differences across hominin species in timing of expression: this could be the case of genes regulated by MEF2A (Liu et al., 2012a), like *CDKL5* (reviewed above) and *RIMKLA*, which encodes N-acetylaspartylglutamate synthetase II, an enzyme synthesizing the neurotransmitters N-acetylaspartylglutamylglutamate and N-acetylaspartylglutamate (Neale et al., 2011). Lastly, differential regulation can arise from poorly understood interactions with the microbiome during development (not just evolution).

MICROBIOTA AND LANGUAGE EVOLUTION

The impact of microbiota in the host (neuro)development transcends the effect of horizontally-acquired genes. Accordingly, we should expect some impact on language evolution (**Figure 1**). Microbiota may modulate the host transcriptome via the interaction with RNA editing enzymes (Schellekens et al., 2012) or RNA methylation enzymes (Zheng et al., 2013), its effects on histone acetylation levels (MacFabe et al., 2011) or its mimicry of the host epigenetic machinery via specific proteins (Bhavsar et al., 2007) or ncRNAs (Liu et al., 2012b). The microbial and host genomes can be regarded as an extended genome or *hologenome*, as the former complements missing components of the latter (see Rosenberg and Zilber-Rosenberg, 2014). We should thus study the genomes of our microbial endosymbionts if seeking a full account of the language gene network (or *language hologenome*). For example, changes in the gut microbiota may have allowed changes in the gastrointestinal tract that contributed to the emergence of larger brains within the primate lineage (Aiello and Wheeler, 1995). Moreover, since different microbiota are maintained by closely related species in the same environment (Franzenburg et al., 2013), cognitive differences between closely related hominin species may be partially due to the effect of differential microbiota on brain development and function. Language has a social dimension that affects its acquisition by children and perhaps some of its core properties; interestingly, changes in the social environment affect the individual microbiota and the immune response (O'Mahony et al., 2009). Importantly, recent research suggests that viruses too are part of the microbiota (Virgin, 2014).

At the same time, because they are easily transmissible, aspects of social behavior may have evolved to facilitate the transfer of beneficial microbes that protect from pathogens (Lombardo, 2008; Montiel-Castro et al., 2013, 2014). Cognitive diseases involving social dysfunction (e.g., autism) entail alterations in microbiota composition and function, as attested in humans (Ming et al., 2012) and animal models for the diseases (Hsiao et al., 2013; Desbonnet et al., 2014). There seems to also exist a critical period for the acquisition of microbiota-dependent social abilities, because some time after weaning,

germ-free animals that lack social cognition are unable to achieve conspecific recognition memory even after microbiota replenishment (Desbonnet et al., 2014). As Stilling et al. (2014b: p. 11) puts it, "the microbiome represents a further interface for environmental influence and a dynamic source for transgenerational developmental regulation [M]icrobiota … accelerate short-term environmental adaptation and may be especially helpful in unifying different theories of host-microbe co-evolution and the evolution of the 'social brain'." In short, we expect the microbiota to account for some aspects of the "cultural niche" that allowed the transition from modern cognition to modern behavior and thus full-fledged languages.

FROM BRAIN REWIRING TO LANGUAGE EVOLUTION

What is, in the end, the connection between the "wetware" and "mindware" that results in observed behaviors, whether low-level activities of bacterial genes or the high-level accomplishments of human cognition and culture? After reminding us of the Synaptic Plasticity Hypothesis (SPH, that during memory formation, synapses undergo activity-dependent alterations), Gallistel and King (2009; p. 278 and ff.) separate (a) the role of extracting behavioral *information* from an animal's experience from (b) the ability to *carry this information in time* in a computationally accessible format. Rejecting the idea that SPH entails synaptic conductance, they suggest that memory should be implemented "at the sub-molecular level": "Given how much of the requisite machinery is already realized … in DNA and RNA … [It would be] … curious if a basic function that could be better implemented at the lowest possible level of structure … were found to be implemented instead at the circuit level, … requiring orders of magnitude more physical resources." They then emphasize the speed of neural computation, particularly "given that signals travel eight orders of magnitude more slowly in the nervous system than they do in a conventional computer." It is worth clarifying this point.

Presupposed throughout this work is the Computational Theory of Mind (CTM; Fodor, 1975, 1994, 1998): the mind can be seen as an information-processing system, "thinking" being a computational process (a logical manipulation of symbolic representations). In a system of this nature, as Gallistel and King put it: "most of the signal flow is to and fro between memory, where the symbols reside when not entering computations, and the processing machinery that implements [them]". They then reason: "Given that signals travel slowly in neural tissue, the only way to minimize the time consumed in transferring information from memory to the processing machinery and back again is to place … memory [and] processing machinery as close together as is physically possible." After quoting Feynman's (1960) dictum that "There is plenty of room at the bottom," Gallistel and King conclude that, in a neurobiological context this pushes the computational system to the realm of nucleic acid … Gallistel and King are not speaking of human cognition—they are analysing animal cognition in general. If the place to carry information forward in time within animal minds is "at

the bottom", that should be where the evolution of complex computation, of the sort presupposed in language, must have proceeded; this of course is the idea behind the "immune syntax".

Second, it is worth noting some of the parallels that exist between the well-known properties of the immune system and NS as presently understood, as advanced by Piattelli-Palmarini and Uriagereka (2004) and see Piattelli-Palmarini and Uriagereka (2008):

1. Adaptive immunity creates immunological memory after an initial response to a specific pathogen, and leads to a response to subsequent encounters with that pathogen. Similarly, the computational system creates a lexical memory after an initial response to an acquired word, allowing for a recall to subsequent encounters with that very word.
2. There are two main classes of adaptive immune responses: antibody responses and cell mediated immune response that are also carried by two different lymphocytes (B cells and T cells). Similarly, there are two main broad classes of words: nouns and verbs, which are arguably carried by two different lexical dimensions.
3. Pathogen-specific sensors are "acquired" during the lifetime of the organism (the acquired response is said to be "adaptive" because it prepares the body's immune system for future infections). Similarly, lexical items are acquired during the lifetime of the human organism (the acquired response could be said to be "adaptive" in that it prepares the linguistic system for future encounters with words).
4. Because of accelerated somatic mutations and irreversible genetic recombination of antigen receptor gene segments, a few genes generate a vast number of different antigen receptors. Similarly, because of Merge, a few lexical items generates a vast number of different sentences.

This may be just a case of convergent evolution, but it may be well an example of real crosstalk between the immune system and the brain. Piattelli-Palmarini and Uriagereka went into further similarities, but since presenting those would require us to delve more deeply into the nature of NS computations, (1) through (4) are enough to make the point. Coincidences or metaphors? Perhaps. During the last 150 years, neurolinguistics has attempted to map language to the brain, usefully so. Nonetheless, as Poeppel (2012) notes, mapping is not explaining. Key components of our description of language, even those as basic as memory, are still elusive. Currently, neurolinguistics is trying to distill language into a set of computational primitives (otherwise not specific to language) that form the basis for more complex representations and computations. Our speculation should be seen in that light.

One promising approach is the decomposition of language into a suite (or grammar) of endogenous brain rhythms (see Giraud and Poeppel, 2012 on speech). Brain oscillations are primitive units of brain function and are conserved across species while, at the same time, vary across disorders (Buzsáki and Watson, 2012; Buzsáki et al., 2013). Because we agree with Gallistel and King that whatever goes on "at the bottom" (nucleic interactions and more) may be closer to the CTM than the still vague associations of neurophysiology, it may worth exploring this complex parallel play between the immune system, the brain, the genome, and the microbiome.

CONCLUSIONS

The complex evolutionary process resulting in the emergence of syntax (language in a complex sense) did not only depend on mutations occurred in particular genes, important for brain development and function. As noted by many (Enard et al., 2002; Khaitovich et al., 2006; Sikela, 2006; Vallender et al., 2008; Varki et al., 2008), most such mutations probably affected the transcriptome, involving changes in the epigenetic landscape of the primate brain. In this article, we have built on a hypothesis put forth by Piattelli-Palmarini and Uriagereka, "the immune syntax", to explore another source of variation that may have contributed to the emergence of modern cognition and language: host-pathogen(-like) interactions occurred during evolution.

Because of the growing interest in genes potentially involved in language evolution, we have focused on genes that may have been transferred by other organisms to the human genome (though other mechanisms may have played a role). Literature-based assembly of gene-to-gene interactions (and their evolutionary consequences) has limitations. The links we have highlighted must be experimentally tested in ways that we ourselves cannot undertake, in order to prove their putative biological meaningfulness regarding brain development and cognitive evolution. Some sources of evidence we have used are stronger than others (e.g., data on direct protein to protein interactions as compared to data on genes that are up- or down-regulated after gene transfection). We also expect the vast literature and datasets to be selectively biased as they focus on given genes, processes, or different methods of interest. As a consequence, the genes we have highlighted should be regarded as mere *candidates for future research*.

We believe the links reviewed are robust in light of our current knowledge of the biological underpinnings of the language faculty, and meaningful for research on its evolution. For all its admitted limitations, our research may offer signposts for the future of this topic, at a stage of research in cognitive biology that is early enough to be fascinating, but hopefully not too early to be reckless.

AUTHOR CONTRIBUTIONS

AB-B explored the molecular and physiological links between the immune system and the brain, gathered the genetic data, and established the relevance of the genes under discussion for language evolution. JU authored the original hypothesis and reinterpreted it according to the biological evidence.

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