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Language development and disorders: Possible genes and environment interactions

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ABSTRACT

Language development requires both basic cognitive mechanisms for learning language and a rich social context from which learning takes off. Disruptions in learning mechanisms, processing abilities, and/or social interactions increase the risks associated with social exclusion or developmental delays. Given the complexity of language processes, a multilevel approach is proposed where both cognitive mechanisms, genetic and environmental factors need to be probed together with their possible interactions. Here we review and discuss such interplay between environment and genetic predispositions in understanding language disorders, with a particular focus on a possible endophenotype, the ability for statistical sequential learning.

1. Language development and disorders

In the first years of life, children develop a set of highly complex skills that together allow them to comprehend speakers around them and communicate actively with them. Human language and communication are considered unique to the human species, and include the ability to produce and arrange sequences of speech sounds into hierarchically structured patterns that refer to abstract, not immediately perceivable concepts (Tomasello, 2010). Being such a complex ability, language requires several lower order processes to be developed progressively, and typically developing children need at least four to five years to acquire a basic fluent control of language (Hoff, 2015; Onnis, 2017). Both basic cognitive abilities and sustained massive exposure coupled with communicative interaction with caregivers are required for success. Understanding the typical adaptive paths to language acquisition becomes even more important when examining the effects of language disorders. When the learning process is disrupted, language outcomes can be affected or even impaired. The consequences of this may be evidenced across several developmental domains because language functions are the channel through which children learn social abilities and receive academic instruction, allowing for cognitive functions to reach adulthood levels.

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Table 1
Main language developmental disorders and associated genes.

Disorder	Affected genes	Common comorbidity	Language abilities	Intelligence
Developmental verbal dyspraxia	FOXP1 (Hamdan et al., 2010)	ASD	Articulation difficulties in producing consonants and vowels	Normal non-verbal IQ
	FOXP2 (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001)	Epilepsy	Overuse of one sound	
	16p11.2 in Chromosome 16, found in 16p11.2 microdeletion disorder (Raca et al., 2013)	Traumatic Brain Injury	Inappropriate prosody affecting stress, intonation and phrase boundaries	
	GALT in Galactosemia (Webb, Singh, Kennedy, & Elsas, 2003)		Inappropriate lengthening	
Specific Language Impairment	CNTNAP2 (Vernes et al., 2008)	ASD	Articulation difficulties, e.g. simplified speech with reduced consonant clusters	Normal non-verbal IQ
	CMIP and ATP2C2 (Cope et al., 2005; Falcaro et al., 2008)		Omission of grammar features, e.g. subject-verb agreement	
Dyslexia	DCDC2, KIAA0319 and 6p21 on chromosome 6 (Fisher et al., 1999; Francks et al., 2004; Schumacher et al., 2006)	ADHD	Lack of phonological awareness, with difficulties in identifying or generating rhyming words or counting syllables in words	Normal non-verbal IQ
	DYX1C1 on Chromosome 15 (Bates et al., 2010; Taipale et al., 2003)	Developmental Coordination Disorder	Difficulties in orthographic coding, which usually result in poor spelling and reading skills	
Stuttering	GNPTAB, GNPTG and NAGPA (Kang & Drayna, 2011)	ADHD	Speech disfluency, including repeating sounds, syllables or words and silence or prolongation of sounds	Normal Intelligence
	Chromosome 15 (Wittke-Thompson et al., 2007)	Tourette Syndrome		
	Chromosome 18p (Shugart et al., 2004)			

Table 2
Language abilities in genetic disorders.

Disorder	Affected genes	Language ability	Common comorbidity	Intelligence
Down Syndrome (Silverman, 2007)	Extra copy on chromosome 21	Weak expressive language, morpho-syntactic processing, and verbal working memory, Delayed language and speech development	Highly social, engaging and affectionate	Mild-to-moderate intellectual disability
Williams Syndrome (Mervis et al., 2000)	Deletion of CLIP2, ELN,GTF2I, GTF2IRD1,LIMK1 on Chromosome 7	Intact	Hypersocial Reduced visuospatial cognition	Mild-to-moderate intellectual disability
Prader-Willis Syndrome (Cassidy et al., 2009)	Chromosome 15 deletion 15q11-13 on paternal side	Language development delayed and impaired Articulation problems	Difficulties recognizing facial expressions of emotion and social intent	Mild-to-moderate intellectual disability
Angelman Syndrome (Micheletti et al., 2016)	Chromosome 15 deletion 15q11-13 on maternal side	Almost non-verbal Severe impairment of receptive and expressive skills	Overly social usually with spontaneous laughter	Mild-to-moderate intellectual disability
Wolf-Hirschhorn Syndrome (Fisch et al., 2008)	Chromosome 4 deletion involving NSD2, LETM1 MSX1	Some individuals are nonverbal	Relatively strong social ability	Mild-to-moderate intellectual disability
Smith-Magenis Syndrome (Madduri et al., 2006)	Chromosome 17 deletion RAI1 involved	Stronger auditory memory and processing for linguistic tasks as compared to formulation Receptive vocabulary is stronger than expressive, knowledge of word associations is better than syntactic skills	Good pragmatic skills	Mild-to-moderate intellectual disability
Turner Syndrome (Hong et al., 2009 Hong, Kent & Kesler, 2009)	X deletion	Intact	No social cognitive impairment	Normal intelligence
Fragile X Syndrome (Finestack, Richmond &Abbeduto, 2009)	FMR1	Intact	ASD is a common comorbid condition	Mild-to-moderate intellectual disability
Cri du chat Syndrome (Mainardi, 2006)	FMR1	Some individuals can only express themselves in few basic words, gestures or sign language	Usually friendly and enjoy social interaction	Mild-to-moderate intellectual disability

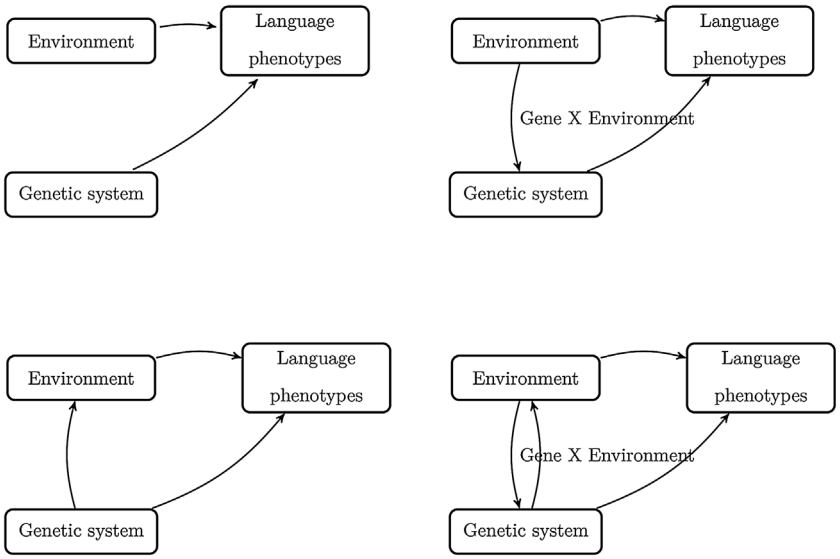

Fig. 1. Four conceptual models of the role of genes and environment (here, caregiver communication) in emerging language disorders. Top left: Environment and genes contribute independently to language disorders. Bottom left: Genetic predispositions constraint linguistic input. Top right: Environment has an epigenetic effect on genetic expressions of the language phenotype. Bottom right: Genes and Environment affect each other in determining language outcomes.

There has been an intense effort to understand the genetic bases of language and language disorders (de Zubicaray & Fisher, 2017). One of the challenges in arriving at a full picture is that language disorders come in different forms and can have different causes. At the phenotype level, as a first approximation, we can distinguish between the set of disorders that appear to affect specific language abilities, while maintaining other cognitive and social skills relatively intact, versus broader disorders that also implicate forms of language delay or disruption. Within each of these two broad categories, one can further dissociate specific disorders, and an open question is the extent to which they stem from similar or different underlying causes. For example, among disorders limited to language (Table 1), verbal dyspraxia (the inability to perform the orofacial movements necessary for articulation only when producing language), Specific Language Impairments (SLI) and dyslexia appear to be linked with difficulties in either learning statistical structure or executing sequential aspects of language. Other language-related disorders (Table 2) can be found in Autistic Spectrum Disorders and may emerge from different reasons, including limitations in the adaptive social interactions necessary to acquire language, which in turn may limit the ability to pay attention to linguistic information the child receives.

In addition, language impairments are not always in comorbid condition with developmental disorders, which exhibit different patterns of linguistic strengths and weaknesses. For example, when comparing individuals with Down syndrome and Williams syndrome, both feature hyper-sociality (Hickey, Hickey, & Summar, 2012; Lashkari, Smith, & Graham, 1999), mild intellectual disability (Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000; Weijerman & De Winter, 2010), and spatial deficits, with individuals with Williams Syndrome being poor on global organization and individuals with Down Syndrome being poor on internal details (Bellugi, Lichtenberger, Mills, Galaburda, & Korenberg, 1999). However, language impairment is only found in Down Syndrome and mainly spared in Williams Syndrome (Thomas & Van Herwegen, 2014). Language abilities appear intact in children with Williams Syndromes, in terms of semantics, morphology and phonology (Carrasco, Castillo, Aravena, Rothhammer, & Aboitiz, 2005). Conversely, language and speech impairments are common in Down syndrome children, who exhibit articulation problems and delayed development in semantics, phonology, syntax and pragmatics (Martin, Klusek, Estigarribia, & Roberts, 2009; Roberts, Price, & Malkin, 2007).

In the study of the genetic bases of language disorders, it is reasonable to first assume that different phenotypes have different genetic bases. However, classification of disorders based on phenotypic distinctions may in some cases obscure common underlying cognitive mechanisms, and their genetic bases. Furthermore, the genetics of language has so far been mainly studied without considering gene × environment interactions (G × E). These occur when the effect of the environmental exposure on a certain outcome is strongly influenced or contingent upon genotype and vice versa. The effects of modified language experiences on the genetics of language disorders are largely unknown. These considerations suggest that to investigate language as a complex ability involving lower as well as higher order processes, it is necessary to adopt a multilevel approach.

Given the above considerations, the present review takes into account basic cognitive, genetic and environmental factors, and suggests some new specific ways in which they may dynamically interact to influence atypical language development. The review unfolds in four main sections and a conclusion. The first section considers recently proposed underlying mechanisms of language acquisition, as they are known under the terms statistical/sequential/procedural/implicit learning. Despite differences in terminology and detail in theoretical orientation, the common denominator is that language acquisition is linked to the remarkable ability to discover statistical regularities and patterns in sequences of spoken and written words (Christiansen, Conway, & Onnis, 2012). In this

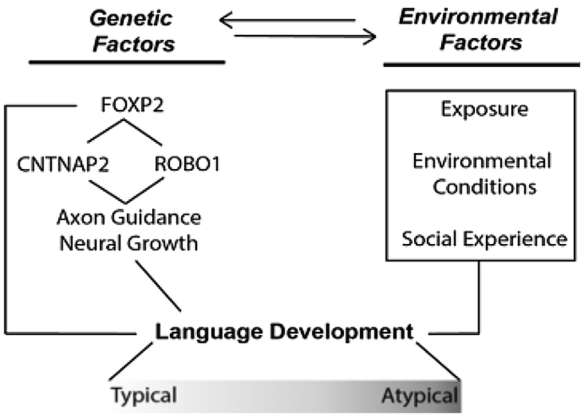

Fig. 2. Representation of direct and indirect effects of some relevant genetic and environmental factors on language development and of the interaction between them. The overall summation of all the factors, both due to direct relations or to interactions, results in language developmental profiles that fall into a continuous spectrum of possibilities, from complete typical to highly atypical development.

review we refer to these terms interchangeably, to highlight both the implicit and automatic (procedural) nature of these mechanisms, and the probabilistic and temporal nature of linguistic information upon which these mechanisms must operate. Most relevant to the present review, a growing number of studies show an association between language impairments and deficits in statistical learning tasks.

The second section reviews candidate genes associated with language abilities and disabilities, taking into account their underlying genetic mechanisms. In particular, we note that several genetic variants that occur in language disorders are also generally involved in the ability to process sequential information. This suggests that sequential learning may constitute a useful candidate endophenotype for language disabilities.

The third section documents the role of environmental experiences in triggering adaptive language development – in particular the language input and communication interactions between child and caregiver, with a focus on how caregivers can mediate the quantity and quality of linguistic statistical patterns presented to the child in their input. The fourth section provides a selection of possible gene × environment interactions. For example, because language appears to be linked to the ability to procedurally discover statistical regularities and patterns in speech, parents providing richer statistical input to the child may boost the genetic bases of procedural learning. We conclude by proposing a conceptual framework for pursuing new research on G × E interactions.

2. What the child brings to child language I: sequential learning abilities

2.1. Sequential learning in language development

Cognitive mechanisms of sequential learning have been proposed to be at the basis of the discovery of language. They all entail the detection of patterns in the environment at progressively higher-order levels of linguistic sophistication – from phonetic–phonemic, to lexical and phrasal/sentential – as well as the ability to abstract and generalize over such patterns. At the phonemic level, children first must learn to partition sounds that vary along many dimensions (such as speaker, rate, or context) into phonemic categories. The role of exposure to language begins in utero, when the peripheral auditory system matures and the fetus has access to her first linguistic inputs as early as 26 weeks of gestation (Eisenberg, 1979). Having been exposed to speech in the womb, newborns can already distinguish speech sounds of their own mother tongue from others belonging to a different language (Moon, Lagercrantz, & Kuhl, 2013). As young as four months, infants then become able to discriminate speech sounds vs non-speech sound (Minagawa-Kawai, Cristiá, & Dupoux, 2011). At about six months of age, infants can discriminate virtually all phonetic contrasts in natural languages (for a review see Aslin, Saffran, & Newport, 1998). At the same time, by the first year of life, infants' ability to universally distinguish phonetic units such as */p/* versus */b/* gradually narrows to the language(s) that they are systematically exposed to – a process termed perceptual narrowing (Kuhl, 2004; Werker & Tees, 1984). This change in the decline of precision in speech perception is believed to be an earlier form of brain specialization mediated by the environment and indicates that infants tune into the input properties specific of their language (Gomez & Gerken, 1999; Kuhl, 1993). Such properties involve frequency distributions, conditional probabilities, variation versus stable features, even absence of expected frequencies, and more. For example, the distribution of speech properties such as voice onset time (VOT) allow infants to discriminate phonetic categories (Maye, Weiss, & Aslin, 2008; Maye, Werker, & Gerken, 2002). Infants from English speaking homes were better able to discriminate boundary sounds (/ta/ vs /ka/ or /ta/ vs /ti/) since English VOTs have bimodal distribution, whereas infants exposed to a language that has unimodal distribution could not.

Between 8 and 12 months infants start babbling, learning and practicing the articulatory movements necessary for the pronunciation of target phonemes. These movements require the sequential coordination of nearly 100 individual muscles. From the first year of age onwards toddlers learn to understand and produce words and grammatical structures at an increasing rate, a process that

peaks during the third year of age (Butterworth, 2014). At that age another non-trivial task is to discover the acoustic forms of a word. Running speech rarely contains words in isolation (Brent & Siskind, 2001); and word boundaries are not marked by clear pauses (Cole & Jakimik, 1980). In word segmentation, distributional information enables infants to identify words and phrases that are not clearly marked in speech. Infants as young as 7.5-month-old are able to recognize words from familiar speech (Jusczyk & Aslin, 1995). Infants can use prosody and intonation information to determine phrasal boundaries (Pannekamp, Weber, & Friederici, 2006). Analyses of databases of child-directed speech suggest that young infants rely on distributional cues in their caretakers' speech to determine the category of a certain word (Mintz, Newport, & Bever, 2002). For example, Mintz (2003) showed that frequently used productive patterns in child-directed speech such as *you_it, the_one* could enhance children's acquisition of the lexical categories that were embedded in such patterns. In addition, studies on artificial language learning also indicate that infants as young as 12 months of age can use distributional cues to group words that have no semantic meanings into categories (Gerken, Wilson, & Lewis, 2005; Lany & Gómez, 2008). Clair, Monaghan, and Christiansen (2010) combined bigrams and trigrams (e.g. aX, aXb) and recategorized them into flexible frames (e.g. aX + Xb), to explain more acquisition data. Given that learners are sensitive to different probabilistic cues and must integrate them in complex ways, Thiessen, Kronstein, and Hufnagle (2013) proposed an Extraction and Integration framework, where the extraction component refers to the ability to discover patterns in the input, and is mediated by attention and working memory (Perruchet & Tillmann, 2010). Integration involves processing extracted information to identify primal information, which may rely on hippocampal structures and long-term memory (McClelland, McNaughton, & O'reilly, 1995; Thiessen & Pavlik, 2013). Before asking which genes might underlie statistical sequential learning for language, we turn to evidence of sequential learning deficits in language disorders.

2.2. Sequential learning in language disorder

Studies of clinical populations can provide further insights on the relation between statistical sequential learning and language development. One direction is to obtain within-subject correlations between language deficits and impaired sequential learning in populations with known language disorders. Furthermore, if these populations were found to have either language or statistical ability intact while the other skill impaired, one could draw the implication that the specific language deficits rely on other cognitive abilities. Impairment in implicit learning or procedural learning ability is usually found in language disorders, for example in Specific Language Impairment (SLI), a strongly genetic disorder that exhibits great heterogeneity (Bishop, 2009; Leonard, 2014). Many individuals with Specific Language Impairment also exhibit nonlinguistic deficits including fine motor control deficits involving sequences of movements. School-aged children with SLI performed at chance in segmenting speech based on statistical structure, compared to a control group matched for non-verbal IQ who performed significantly better than chance (Evans, Saffran, & Robe-Torres, 2009). SLI children and adolescents also showed slower learning rates compared to typically developing peers on non-linguistic implicit learning tasks (a Serial Reaction Time Task requiring detection of adjacent and nonadjacent regularities), indicating impaired implicit learning ability (Lum, Conti-Ramsden, Page, & Ullman, 2012; Tomblin, Mainela-Arnold, & Zhang, 2007). The deficits in implicit learning and language processing imply that impaired statistical learning ability could be the cause for both deficits (Erickson & Thiessen, 2015). Similarly, impaired implicit learning ability was also found in children diagnosed with developmental dyslexia (Hedenius, Ullman, Alm, Jennische, & Persson, 2013; Lum et al., 2013; Pavlidou and Williams, 2014 Pavlidou & Williams, 2014). Furthermore, in Christiansen, Kelly, Shillcock, and Greenfield (2010) a breakdown of language in agrammatic aphasia was also associated with an impairment in sequential artificial grammar learning, in a study comparing agrammatic aphasic patients and control participants matched for age, socioeconomic status and non-verbal intelligence.

Finally, if language acquisition is subserved by sequential learning mechanisms, relative language strengths in a specific genetic disorder should also correlate with spared statistical learning skills. Indeed, this appears to be the case in Williams syndrome, in which language development is delayed, but accelerates during adolescence. Most language abilities end up in line with overall mental age (Carrasco et al., 2005). Likewise, infants with Williams Syndrome showed no deficits of detecting statistical regularities in speech (Cashon, Ha, Estes, Saffran, & Mervis, 2016). Performance on artificial language learning tasks also showed that adult individuals with William Syndrome exhibited implicit learning ability on a par with a control group matched for non-verbal intelligence (Don, Schellenberg, Reber, DiGirolamo, & Wang, 2003). Thus, the studies conducted so far on sequential learning and language disorders suggest that not only does the reduced statistical learning correlate with language delays, but typical statistical learning is found in disorders exhibiting no substantial language deficits.

3. What the child brings to child language II: genetic bases of language

As a higher-order cognitive process language recruits lower order processes such as sequential learning, working memory, and the ability to socially communicate. For this reason, researchers in the last 20 years have not only investigated the relation between different genotypes and the phenotype of language disorders but they have also considered the genetic basis underlying the endophenotypes related to language processes. Here, we focus on those endophenotypes associated with sequential learning, as well as social communication abilities that might impair the ability to extract statistical information from child-directed speech.

3.1. Genes for sequential learning

As we have seen, sequential learning, also referred to as procedural, implicit, or statistical learning (henceforth SL) is the ability to unconsciously identify, extract, and abstract over sequences and recurrent information in the environment (Romberg & Saffran, 2010;

Saffran, 2003). SL is believed to be involved in several cognitive tasks, such as language and numeric processing. Similarly, an important role for sequentially encoded information is posited in Baddeley's model of working memory (Baddeley, 1992). Specifically, the phonological loop deals with spoken and written material, holding sequential information in a speech-based form (i.e., spoken words) for 1–2 s during speech perception, and is used to rehearse and store sequentially ordered verbal information in the generation of articulatory gestures for speech production. Given the importance of these two endophenotypes for language processes – sequential learning abilities and phonological loop in memory – researchers have studied their relation with genetic predispositions linked to language disorders. The FOXP2 gene, for instance was found to be highly involved in language production (Lai et al., 2001), and has also been found to be related to sequential learning processes. FOXP2 codes for a forkhead-domain protein expressed in the central nervous system and, as other genes of the FOX family, it is involved in embryogenesis. Interestingly FOXP2 appears to be phylogenetically highly conserved within mammals. Specifically only two amino acids out of 715 differ between humans and chimpanzees and three between humans and mice (Enard et al., 2002). The gene FOXP2 was found to be non-functional in a child, CS, and in many members of the KE family, who suffered from a severe orofacial dyspraxia present only during language production, inability to break up words into their constituent phonemes and disrupted grammatical skills, both during production and comprehension. The gene functionality was affected because of a translocation. A translocation occurs when part of a chromosome switches place with a piece of a different non-homologous chromosome. Within the KE family all the members affected by the language disorder carried the FOXP2 genetic translocation, while between the non-affected members no one presented it. Furthermore, the causal role played by FOXP2 in language processes has been corroborated in animal models. Mice knockout for the FOXP2 gene vocalized less, produced shorter syllables and displayed an arrhythmic vocalizations' structure compared with their typical developing littermates (Castellucci, McGinley, & McCormick, 2016). The relation of FOXP2 with other language disorders, however does not seem to be directly involved or associated with other disorders, such as SLI, ASD or dyslexia (Kang & Drayna, 2011; Meaburn, Dale, Craig, & Plomin, 2002; Newbury et al., 2002). Therefore FOXP2 is highly involved in language production, but it does not directly regulate language abilities altogether. Recent research rather points to the involvement of FOXP2 in endophenotypes underlying language abilities: sequential learning and phonological buffer's performances. Chandrasekaran, Yi, Blanco, McGeary, and Maddox (2015) found that individuals homozygotes for the G allele in the region rs6980093 of the FOXP2 gene, known to be involved in the modulation of prefrontal cortex activity during speech processing, adopted more efficient cognitive strategies in teaching themselves to categorize pitch dynamics belonging to a novel language (Chandrasekaran et al., 2015). In addition, members of the KE families affected by SLI tested for working memory functions were found to be specifically impaired in phonological loop-related tasks, but not to be impaired in central executive or visuospatial sketchpad performances compared to non-affected members of the family and to the control group (Schulze, Vargha-Khadem, & Mishkin, 2018). This further suggests that it is the sequential processing aspect of working memory that was specifically affected in those individuals.

In general, FOX genes are regulatory genes, as they code for proteins that contribute to the expression of other genes, affecting all the processes regulated by FOXP2 gene's downstream biochemical cascade (Vernes et al., 2007). Within FOXP2 gene targets in the central nervous system there exist genes responsible for neuronal organization and axonal growth during central nervous system development (Carlsson & Mahlapuu, 2002). FOXP2 gene expression is restricted to prenatal period in humans and monkeys while it continues up into adulthood in mice (Takahashi et al., 2008; Takahashi, Liu, Hirokawa, & Takahashi, 2003; Takahashi, Takahashi, & Liu, 2009). Therefore, the final phenotype may be drastically different depending not only on which step of the biochemical cascade is affected but also on its timing during development. When FOXP2 is transposed all related cascade processes are affected. Conversely, when only later steps of the cascade are impaired, only some branches of the cascade are affected. Multiple genes have been associated with different language disorders and since multiple abilities are involved even more genetic factors together with their own downstream targets and temporal dynamics may need to be taken into account. Among FOXP2 downstream targets, the gene CNTNAP2 has been found to be associated with SLI, ASD and Speech Sound Disorder (SSD) (Vernes et al., 2008; Zhao et al., 2015). Furthermore, ROBO1 was associated with ASD, dyslexia and SSD (Hannula-Jouppi et al., 2005; Lei et al., 2017; Stein et al., 2004). Again, in recent research these genes are involved in both language disorders and sequential learning and phonological buffer's performances, thus strengthening the evidence for a direct link between the two abilities (Bates et al., 2011; Folia, Forkstam, Ingvar, Hagoort, & Petersson, 2011).

CNTNAP2 codes for a cell adhesion transmembrane protein involved in cell to cell interaction and synchronicity as well as in the determination of neurons and glial cells morphology and density. Mutations in CNTNAP2 have been associated with language impairments at a behavioral level (Newbury et al., 2011) as well as with changes in brain structure (Uddén, Snijders, Fisher, & Hagoort, 2017). In two different studies, two single nucleotide polymorphisms in the regions rs2710102 and rs17236239 of the CNTNAP2 gene were linked to the ability of reading non-words (Newbury et al., 2011; Peter et al., 2011), while a polymorphism in the region rs759178 of the same gene was associated with the reading fluency of non-words (Carrion-Castillo et al., 2017). This core ability is predictive of reading and spelling traits for both normally and atypically developing children with dyslexia. Non-words are phonologically possible but non existent words, therefore the difficulty in encoding and pronouncing them may be linked to specific difficulties in motor programming or execution, which is in line with CNTNAP2 being a target of FOXP2 gene. FOXP2 is in turn involved in the development of orofacial dyspraxia in Specific Language Impairment, highlighting the relevant role that the FOXP2-CNTNAP2 pathway plays in the emergence of language disorders (Vernes et al., 2008). In addition, non-words reading tasks rely on sequential statistical learning abilities and this process has been found to be directly related to CNTNAP2 characteristics (Folia et al., 2011) For instance, T carriers in the region rs7794745 of CNTNAP2 gene were more sensitive to grammatical sequences since they acquired structural knowledge more rapidly while showing at the same time a greater activation in Broca's region (Folia et al., 2011).

Another target of FOXP2 downstream is ROBO1, a gene coding for proteins that contribute to guide axons to their right target, especially for crossing the midline (Long et al., 2004). Bates et al. (2010) identified ROBO1 polymorphisms associated with variation

in the ability to repeat non-words, and the gene is also a candidate for dyslexia susceptibility (Bates et al., 2010). Specifically, a translocation causing a silencing of the ROBO1 gene was found in some individuals of the same family affected by dyslexia (Hannula-Jouppi et al., 2005). Although dyslexia is a learning disorder rather than a linguistic disorder, it relies on language-related brain processes. The ability to retain phonological information in working memory and to generalize it to novel linguistic material such as non-words, are necessary for adaptive reading. Therefore, genetic characteristics found in dyslexic individuals are also relevant to characterize endophenotypes underlying language processes and impairments.

Two regions of ROBO1, namely rs6803202 and rs4535189, were specifically associated with non-word reading scores but not with general reading, spelling and working memory performance, thus highlighting the specific involvement of ROBO1 genetic characteristics in processes of phonological encoding (Bates et al., 2011). In addition, in individuals affected by dyslexia an association was found between regions of the gene KIAA0319 and rapid naming of well-known items and word reading fluency (Carrion-Castillo et al., 2017). Indeed, the allele A in the polymorphism -3GA of the dyslexia susceptibility gene DYX1C1 has been associated with short-term memory deficits in humans (Marino et al., 2007). Specifically, a family-based association test run on children reporting reading difficulties and their siblings showed an association between the presence of the A allele in this region of the DYX1C1 gene and the performance in the Single Letter Backward Span, which measures phonological working memory performances (Marino et al., 2007). Also, mice homozygous for DYX1C1 knock-out showed deficits in learning and memory, whereas non-working memory-related processes, namely auditory and motor abilities, were spared (Rendall, Tarkar, Contreras-Mora, LoTurco, & Fitch, 2017). Knock-out mice could not learn to recognize a novel object or to navigate a maze successfully, whereas they performed as well as typical mice in discriminating acoustic stimuli and in running over a rotarod.

One additional system highly involved in procedural learning and fine motor control necessary for speech production, is the dopaminergic system (Booth, Wood, Lu, Houk, & Bitan, 2007; Enard, 2011). The DRD2 gene codes for the dopamine receptor D2 and is involved in fine motor control, dysfluent speech, stuttering, non-word repetition deficits, and grammar learning (Wong, Ettlinger, & Zheng, 2013). Specifically, Wong et al. (2013) showed that individuals homozygous for the A2 allele were better at learning a concatenative grammar compared to an analogic grammar. The former involves sequence learning strategies such as the addition of syllables with no phoneme changes in order to decline nouns. By contrast, the analogic grammar uses vowel changes to indicate the form of a noun. Performance at concatenative learning also correlated with procedural learning abilities, while analogic learning performance correlated with declarative memory abilities (Wong et al., 2013).

Moreover, direct relations between the DRD2 gene and probabilistic learning scores have been found. Specifically, 9-repetition carriers showed faster reaction times in learning configurations of stimuli with high probability, compared to 10-repetition carriers (Simon et al., 2011). Furthermore, the DRD2/ANKK1 gene complex affects the presence of dopaminergic receptors in the corticostriatal circuit and influences corticostriatal activity and motor control (Lee, Mueller, & Tomblin, 2016). This gene complex was involved in procedural learning although not directly associated with the presence of language disorders. The importance of an adaptive functionality of these dopamine-related circuit and the way they are inter-connected with linguistic processes is highlighted by a research by Enard and colleagues (2009) where a humanized version of FOXP2 knocked in in mice moderated vocalizations' acoustic characteristics and striatal neurons' anatomy. Mice homozygotes for the humanized version of the FOXP2 compared to wild type animals emitted vocalizations with lower fundamental frequency F0, grew longer dendritic trees in striatal neurons, and showed lower dopamine concentration in the caudate-putamen, nucleus accumbens, globus pallidus, cerebellum and frontal cortex, while the concentration of other neurotransmitters, namely glutamate, serotonin, and GABA, was not significantly different between the two groups (Enard et al., 2009).

3.2. Genes and social communication

Language is primarily learned and used in social settings, and thus genes associated with the development of social abilities and communication likely play a role in determining the trajectories of language development and disorders. Because social communication strongly mediates the acquisition of language and the development of language abilities, or language to be acquired, caregiver-child communication needs to be develop adaptively (Markus, Mundy, Morales, Delgado, & Yale, 2000). Therefore, in investigating how genetic predispositions are associated with language disorders, genes involved in the regulation of the acquisition of social abilities are likely candidates for language delays and disorders. For example, Autism Spectrum Disorders involve a spectrum of behavioral characteristics but their core feature is an impairment of social communication abilities (American Psychiatric Association, 2013). This deficit hinders the possibility to build a successful and attuned interaction and communication with caregivers through which the child acquires language. The region rs2710102 of CNTNAP2 gene is associated with the age of the first word in infants affected by ASD (Alarcón et al., 2008). On the structural level, Uddén and colleagues (2017) found that individuals carrying at least one copy of the T allele in the rs7794745 region of the CNTNAP2 gene show reduced gray matter in the left superior occipital gyrus, an association area, compared to AA homozygotes (Uddén et al., 2017). Moreover, this reduction increases with the number of T alleles. Mutations in the ROBO2 gene are also associated with Autism Spectrum Disorders (Anitha et al., 2008; Prasad et al., 2012; Suda et al., 2011). ROBO2 is part of the ROBO family and, as such, it is involved in axonal guidance and brain development (Van Battum, Brignani, & Pasterkamp, 2015). The indirect link between the role played by ROBO2 in language acquisition through the mediation of social communication has been directly highlighted in a study by St Pourcain et al. (2014), who found an association between ROBO2 genotype and the development of expressive vocabulary in human infants (St Pourcain et al., 2014).

3.3. Further directions

New studies are pointing towards new genetic loci of interest related to the development of language impairments or to the anatomy of language-related areas in the brain. For example, recent whole-genome sequencing studies found that variants in newly tested regulatory genes – such as the aforementioned FOXP2 – are related to language impairments and morphological differences in brain areas involved in language processing. Namely the variants classified as pathogenic in the genes CHD3, SETD1A, WDR5, KAT6A, SETBP1, TNRC6B, and ZFHX4 in some individuals affected by Childhood Apraxia of Speech (CSA). Interestingly, these genes are involved in regulatory pathways – coding for proteins recruited in processes such as chromatin remodeling and DNA methylation – and interact with FOXP2 in regulating gene expression Eising et al. (2018). Moreover, variations in the gene RBFOX2, responsible for regulating alternate splicing in the brain has been related to morphological differences, namely cortical thickness in brain areas involved in language processing (Gialluisi, Guadalupe, Francks, & Fisher, 2017). Mutations in the SRPX2 gene, which is regulated by FOXP2 activity and is involved in synaptogenesis, specifically in the formation of excitatory synapses (Sia, Clem, & Huganir, 2013), have been related to the presence of rolandic seizures with associated oral and speech dyspraxia (Roll et al., 2006). Also, knocking down SRPX2 caused atypical electrical potentials in mice and decreased the ultrasonic vocalizations in infant mice (Sia et al., 2013). Further studies will be necessary to unveil the specific role of these genes in the development of brain language centers, sequential learning and language-related motor programming.

4. What the environment brings to child language: caregiver communication

In the last 40 years or so, several lines of research have provided mounting evidence that caregiver speech plays a fundamental role language development. For example, evidence has accumulated in the development of phonetics and phonology that caregivers adapt their language in a manner that seems to make the language learning task easier for children. This way of communicating is referred to in the literature as “motherese”, “parentese”, child-directed speech (CDS), or infant-directed speech (IDS) (for a systematic review, see Saint-Georges et al., 2013). For example, adults often speak to infants and young children in a speech style that is slowed down, contains longer pauses, shorter sentences, and a wider range of pitches (Harley, 2017). Such a modified style (compared to adult-adult conversation) facilitates language acquisition in many aspects including the discovery of words in connected speech (Thiessen, Hill, & Saffran, 2005), lexico-syntactic patterns (Goldstein et al., 2010; Waterfall, Sandbank, Onnis, & Edelman, 2010), grammatical categories (Mintz, 2003), and sounds-meaning mappings (Graf Estes & Hurley, 2013). In addition, child-directed speech contributes to learning social cues (Schachner & Hannon, 2011).

Unfavorable linguistic environments can reduce the potential for language. In the 1990s, it became apparent that a child's early language environment is critical to the life-course trajectory of child vocabulary. A landmark study found that reduced exposure to language provided by parents dramatically affected children's language development. Hart and Risley (1995) observed a positive relation between the amount and quality of parent talk and the children's vocabulary size across families from different demographic backgrounds. In particular, by the age of four, 30 million fewer words would have been heard by a child from a poor home, compared with children whose parents are professionals. The seminal finding of Hart and Risley included a small sample size, but has been corroborated by a number of independent studies, and it is now well established that children from low socio-economic status (SES) backgrounds are more likely to experience language delays than their high-SES peers (Brito & Noble, 2014; Hoff, Laursen, & Tardif, 2002; Noble, McCandliss, & Farah, 2007; Noble, Norman, & Farah, 2005). For example, the amount of child-directed speech predicted typical children's receptive vocabulary at 30 and 42 months (Rowe, 2008).

In addition to the quantity of language input, content and quality of language input also affect child language development. In one study (Hoff & Naigles, 2002) the number of different words, the mean length of utterance, as well as the syntactic complexity of maternal speech predicted productive vocabulary in typically developing 2-year-olds. Thus, not only the quantity but also the quality and diversity of words that parents use is associated with the size of children's expressive vocabulary. One serious possibility is that large differences in linguistic skills emerge very early during infancy and childhood, and persist throughout the life of an individual. The work of Marc Bornstein and colleagues shows this to be the case in low- as well as high-SES families starting in the second year of life and continuing to adolescence (Bornstein, Hahn, Putnick, & Suwalsky, 2014; Bornstein & Putnick, 2012; Fernald, Marchman, & Weisleder, 2013). Research in the stability of individual differences in language clearly indicates that language intervention is late in primary school, when the language gap shows increasing rather than diminishing trends. For example, differences in reading abilities appear as early as first grade and persist despite education (Ferrer et al., 2015) – a finding that is taken as evidence that early pre-school intervention is indeed useful, if not necessary in some cases.

A significant relation between maternal speech input and variation in child language development has also been found in atypical populations. Maternal mean length of utterance (MLU) was predictive of language development for preschoolers with Language Impairments, confirming the importance of maternal language complexity for explaining variation in child language development in 4- to 5-year olds (Stich, Girolametto, Johnson, Cleave, & Chen, 2015). Other studies indicated an adult's influence on a child's language development in children with language impairment. In this regard, studies on input characteristics in children with SLI reported contrasting results. On the one hand, some studies observed an impoverished input to SLI children, in the form of fewer conversational recasts or responses Conti-Ramsden (1990). In contrast, other studies have focused on the role of maternal input in improving language processes in children with SLI, indicating that mothers of these children adjust shared reading conversation in response to their children's language behaviour, similar to what mothers of younger typically developing children do (Barachetti & Lavelli, 2011). For these latter studies, the language that mothers address to their children with SLI during conversational interactions is in tune with their children's language production (see also Majorano & Lavelli, 2014).

What emerges from the brief literature review above is that both typical and atypical linguistic development appears impacted by caregiver speech, and one may in principle expect even larger individual differences when children exhibit atypical paths. In the next section, we envisage possible scenarios of interaction between caregiver communication and genes involved in language development, in particular those that appear to be involved in sequential learning skills.

5. Gene × environment

The set of genes of an individual determines the pool of possible physiological processes available during his/her lifetime, together with initial pre-defined biological structures. In addition, the developmental path of both physiological processes and biological structures is also affected by individuals' own experiences and environmental conditions. By way of example, consider a case in which different climate conditions lead to different levels of food availability in a given environment. During a period of food scarcity young individuals' genetic predisposition to grow tall will not be expressed. More in general, an individual's phenotype, physiological processes and behaviors are the result of a dynamic interplay between genes and environment, which can occur in the following ways: (i) genes can affect phenotype, endophenotypes and exposure to environmental factors, (ii) the environment can affect genetic expression and, (iii) genetic predispositions and environmental factors can moderate each other's effects. Next we consider these three cases in relation to language.

5.1. Genetic effects on phenotype and environment

Genetic characteristics may play a leading role by affecting individuals' phenotype or endophenotypes directly, or by moderating environmental factors. In the case of the FOXP2 gene in the CS patient and KE family (Lai et al., 2001), genetic malfunctioning is directly related to a phenotype with impairments in the language processes. Genetic malfunctioning may also influence language processes indirectly by disrupting one or more of its endophenotypes. For example, one explanation for speech sound disorders (SSD) is failure to learn and form stable phonological representations due to poor phonological memory (Tkach et al., 2011). fMRI evidence supporting this hypothesis shows a hypoactivation in the right inferior frontal gyrus in individuals with history of SSD consistent with a deficit in the phonological loop (Tkach et al., 2011). At the genotype level, regions rs6803202 and rs4535189 of the ROBO1 gene are associated with individuals' performance in reading non-words (Bates et al., 2011). As semantic knowledge cannot be accessed in reading non-words, this task, must heavily rely on the phonological loop of working memory. Thus, it is possible that specific loci of ROBO1 impair phonological sub-processes involved in language acquisition. The deficit in the phonological loop may, in turn, limit individuals' exposure to environmental factors necessary for an adaptive language development. For example, the deficit in retaining complex phonological information could prevent infants from recognizing sequences in the environmental stimuli in input and, thus, the statistical learning necessary for language acquisition would not be triggered for lack of exposure.

5.2. Environmental effects on genetic expression

Environmental factors may determine how genes are expressed. In the bioecological model (Bronfenbrenner & Ceci, 1994; Rutter, Moffitt, & Caspi, 2006) it is highlighted how only within an adaptive environment can differences in phenotypes due to genetic predispositions be individuated. For example, the development of language abilities themselves, or the possibility for a language impairment to be shown, is only possible when infants are exposed to a language, which triggers, or fails to trigger, the expression of the specific behavior. The bioecological model is part of a series of processes that fall under the term *epigenetics*: environmental conditions do not change genes, but can operate on a continuum from triggering their expression to shutting it down. One definition of epigenetics is 'modifications of DNA or associated proteins, other than DNA sequence variation, that carry information content during cell division' (Rice, 2012). Epigenetics is in its infancy and epigenetic mechanisms have begun to be understood primarily in animal models. One line of research has looked at parental/rearing effects, because they are widespread in the natural world from plants to mammals (Maestripieri & Mateo, 2009). For example, different parental signals during mother-offspring interactions in rodents can lead to distinct patterns of DNA methylation (Kappeler & Meaney, 2010). These cascade effects lead to stable changes in gene expression within individual rodents, and can persist in subsequent generations. In humans, Roth and colleagues (Roth et al., 2011) found an association between folic acid intake during pregnancy and the risk of severe language delay at three years of age. Specifically, when women had a supplement of folic acid – known to be involved in regulating the expression of the insulin-like growth factor 2 gene (IGF2) (Steegers-Theunissen et al., 2009) – between 4 and 8 weeks after conception toddlers were less likely to develop a severe language delay at three years of age. This effect is likely specific to language, since absence of folic acid intake had no effect on the risk for gross motor skills delay. Accordingly to the model recently proposed by Mabel Rice, this and other environmental factors, such as maternal diet during pregnancy (Monk, Georgieff, & Osterholm, 2013), might cause a growth signaling dysfunction (GSD) affecting the expression of pivotal regulatory genes such as FOXP2 and CNTNAP2 and, in turn, the emergence of SLI deficits. GSD would interfere with the onset, growth and subsequent deceleration of language acquisition delaying the start of language development in a way that when the language processes are finally triggered, they will not be able to catch up with typical development before the deceleration process kicks-in slowing and, eventually, stopping language development (Rice, 2012).

5.3. Two-way interactions between genes and environment

Another broad class of interactions can take place when genetic predispositions and environmental factors mediate or moderate

each other. To explain this interaction, two models have been proposed: the diathesis-stress model, and the plasticity genes model. The *diathesis-stress model* predicts that some genes may be either protective factors or risk factors in the interaction with the environment, depending on their characteristics and mutations (Rende & Plomin, 1992; Rutter et al., 2006). According to this proposal, two individuals having different shapes of one of these genes, and experiencing a favorable environment will have the same developmental possibilities. However, when experiencing a disadvantageous environment one of the two individuals will be protected – still displaying an adaptive phenotype – while the other will be at risk of developing a maladaptive phenotype.

Little is known about how parental input and parent–child interactions might affect the expression of genes involved in language acquisition and processing. We can however advance possible scenarios. One of these is that differences in style, quantity, or quality of linguistic parental input could differentially affect the typical path to language development according to individuals' genetic predispositions. Language requires the ability to procedurally discover structural regularities and patterns in rapid sequences such as speech sounds and sequences of letters in print – in ways that are largely non-conscious. Because parents appear to mediate the extraction of statistical and structural aspects of language, it is plausible to expect more richly structured parental and caregiver input to positively affect the expression of genes involved in statistical learning in children. For example, we could hypothesize that poor parental linguistic scaffolding coupled with risk phenotypes, such as being homozygotes for the A allele in the region rs7794745 of the CNTNAP2 gene, might increase the probability of a language development delay. AA homozygotes in that CNTNAP2 region are worse at detecting and acquiring grammatical sequences, and exhibit weaker activity in Broca's area compared to T carriers in the same region (Folia et al., 2011). Therefore, the AA genotype coupled with reduced parental scaffolding in the detection and learning of grammatical sequences might increase the probability of developing a language delay, whereas the same parental investment coupled with AT or TT genotypes may not exert any specific negative effect on language development.

One further example of the diathesis-stress model applied to language disorders could be found the case of ASD. Recent research confirmed the important role of linguistic input across both typically developing (TD) and children with Autistic Spectrum Disorders (ASD). Both populations acquire language from the specific structure of parental speech, showing facilitative effects of word frequency, diversity of word use, and complexity of sentence structures Naigles (2013).

On the other hand, some researchers have highlighted parental profiles that differ between typical and atypical children. Are these profiles adaptive or maladaptive? Recent work suggests that parental input to ASD children who are minimally verbal may contain overly simple, highly repetitive input (Naigles, 2013; Onnis, Esposito, Venuti, & Edelman, 2018) when compared to parental speech of typically developing children. This excessive level of repetition may be an involuntary yet maladaptive parental behavior that is not as facilitative for children with ASD as is input that presents a wide variety of lexical and grammatical items. In this case, ASD has an effect on parental behavior, which in turn may affect the language profile of the child. An exposure to highly repetitive input in typically developing children could have little effect on language development, whereas in the case of a risk genotype like ASD, a highly repetitive input might hinder the acquisition of linguistic structures, negatively affecting language development.

A more nuanced scenario of interactions between genes and environment is exemplified by the *plasticity genes model* (Belsky et al., 2009; Belsky & Pluess, 2009a, 2009b). In this model genes may be either favorable or disadvantageous as a function of specific environmental factors, rather than constituting absolute risk or protective factors. That is, a specific allele is not a protective or risk factor per se. It rather enhances individuals' sensitivity to environmental factors becoming either an advantage or a disadvantage according to the environmental conditions the individual faces during development. Conversely, individuals carrying a different allele will be less affected by the same environment. This means that individuals more sensitive to the environment will experience worse developmental outcomes when experiencing a non-adaptive environment, compared to less sensitive individuals. If exposed to an adaptive environment, these same individuals will experience better developmental outcomes compared to less sensitive individuals (Belsky et al., 2009).

The plasticity genes model can help explain why some pools of seemingly disadvantageous genetic mutations have survived natural selection: individually each of them may have favoured traits that proved useful in a specific environment (Bishop, 2009). We can again situate this model with respect to language development and disorders, by considering child-directed speech as the environment to the linguistic child. Consider the case in which different levels of language competence at 2 years of age have been associated with the quality of parent–infant relationship (Murray & Yingling, 2000). The extent to which parental behaviors play a role in toddlers' development – their *susceptibility* to being affected by environmental factors – may be moderated by genetic predispositions. For instance, toddlers carrying genes that increase their susceptibility to the environment may show broader linguistic competences when growing up in a highly stimulating environment, while they may show lower competencies or even impairments when growing up in a poor environment. To our knowledge, this model has not yet being tested for language abilities, however we can see the usefulness of applying this model to make predictions about language development trajectories. Earlier we discussed the implications of the diathesis-stress model applied to the region rs7794745 of the CNTNAP2 gene (Folia et al., 2011). Instead of applying the diathesis-stress model, we can imagine the CNTNAP2 gene behaving as a plasticity gene: in this case the AA genotype would be a sensitivity factor rather than a risk factor. That is, individuals homozygous for the A allele exposed to poor parental linguistic scaffolding may develop linguistic delays compared to T carriers. Consistent with the model, the same individuals exposed to highly adaptive parental linguistic scaffolding might develop better phonological memory compared to the same T carriers – T carriers being less sensitive to either adaptive or maladaptive environmental factors.

6. Conclusions

Language development requires both basic cognitive mechanisms for learning language and a rich social context from which learning takes off. Traditionally, researchers have considered the roles of nature and nurture as independent (Fig. 1, top left panel).

But in recent years advances in genetic studies have shifted the theoretical debate to perspectives where genetic and environmental factors play both direct and indirect roles in language acquisition (Fig. 1, three remaining panels). The relationship between genes and the environment in determining the etiology of language disorders is largely unknown. Optimal and suboptimal developmental courses of linguistic environments in which children are immersed have yet to be fully determined, including their potential interactions with genetic expression. In this review we have considered three possible ways that gene × environment interactions could play out: (i) genes moderate environment exposure; (ii) the environment influences genetic expression; (iii) genetic and environmental factors moderate each other's effects on individuals' development (Fig. 2). We have offered a small number of examples of how these interactions may play out, for future studies. The above considerations about the interaction between genetic predispositions and environmental factors are not only applicable to language disorders, but more broadly to the development of typical language abilities in general. Language disorders and typical language development may well constitute two outcomes at the opposite ends of a spectrum involving similar processes. The determination of a specific outcome will ultimately depend on our better understanding of the complex interplay between genes and environment Onnis (2017).

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