The language oscillogenome

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Abstract: Language has been argued to arise, both ontogenetically and phylogenetically, from specific patterns of brain wiring. In particular, it can be shown that core features of language processing emerge from particular phasal and cross-frequency coupling properties of neural oscillations; what has been referred to as the language 'oscillome'. It is expected that basic aspects of the language oscillome result from genetic guidance, what we will here call the language 'oscillogenome', for which we will put forward a list of candidate genes. We have considered genes for altered brain rhythmicity in conditions involving language deficits (autism spectrum disorders, schizophrenia, specific language impairment and dyslexia) for which we have confident genome-oscillome-phenome connections. These selected genes map on to aspects of brain function, particularly on to neurotransmitter function. Our aim is to provide biologically robust genome-to-language links that grant causal and explanatory power to brain rhythms with respect to language processing.

Keywords: Autism spectrum disorders; schizophrenia; specific language impairment; dyslexia; neural oscillations; candidate genes; language deficits

1. Introduction

Which genes regulate mental processes? This is surely one of the most pivotal questions in contemporary neurobiology. In their Foreword to a recent volume on birdsong and biolinguistics, Berwick and Chomsky (2015: x) discuss the potential for one particular gene, *FoxP2*, to contribute to debates about the evolution of our most complex mental capacity, language, commenting that '[h]ow far one can drive this genomic work upward into neuronal assemblies – ultimately, the dissection of the underlying circuitry responsible for vocal production – remains to be seen'.

The present paper will serve as the next step in this biolinguistic approach to language, documenting the genes implicated in oscillatory activity during language processing as a means of establishing robust, causal genome-oscillome linking hypotheses. As is standard in candidate-gene approach studies, we have examined cognitive conditions entailing both language deficits and oscillatory anomalies as a way to identify promising candidates. We have focused on schizophrenia (SZ) and autism spectrum disorders (ASD), which entail language impairment mostly at the syntax-semantics interface, and also on specific language impairment (SLI) and developmental dyslexia (DD), which entail language impairment mostly at the syntax-phonology interface. For a proposal of how to explain these deficits in oscillatory terms, see Benítez-Burraco and Murphy (2016), Murphy and Benítez-Burraco (2016), and Jiménez-Bravo et al. (2017). At the core of these proposals is the assumption that particular computational and representational properties can be attributed to neural oscillations. This continues a recent line of research which has drawn the following conclusions: Computational operations of language can be decomposed into generic processes (Murphy 2015a); these generic processes interact in dynamic ways and can be implemented via neural oscillations (Murphy 2015b); these oscillations implement a multiplexing algorithm for the combination and interpretation of linguistic representations (Murphy 2016a); this multiplexing algorithm appears to be species-specific (Murphy 2016b). The long-standing conclusions concerning the

species-specificity of language therefore come full circle through a human-specific oscillatory code. What we have argued is that, in essence, although most of the nerve tracks and regions which differ in these pathological conditions are implicated in language processing, neural oscillations provide a more reliable explanatory level of the language deficits exhibited by the affected populations. Moving beyond this now requires an examination of the genes responsible for the brain's oscillatory behavior.

The genetic basis of neural oscillations more broadly likely stems from regulatory genes controlling the brain's neurochemistry (Begleiterand Porjesz 2006). Oscillations represent highly heritable traits (van Beijsterveldt et al. 1996, Linkenkaer-Hansen et al. 2007, Hall et al. 2011) that are an interesting combination of being less complex but more proximal to gene function than standard cognitive or diagnostic labels. In what follows, we first provide a functional characterization of candidate genes for the language oscillogenome, with a focus on their biological significance and functions. We then discuss the contribution of these genes to language processing, and sketch genome-to-oscillome-to-language links. With this aim, we will consider the brain areas in which they are expressed, the brain rhythms they have been related to, and the role of these areas and rhythms in language processing. Our goal is to understand how these genes contribute to language processing and how mutations in these genes result in language impairments, with a focus on normal or abnormal oscillatory activity. We conclude with a brief discussion concerning future perspectives for finding more robust links between genes, brain rhythms, and language.

2. A draft of the language oscillogenome

In order to achieve our objective of drafting the language oscillogenome, we first gathered via systematic literature review and database searches an extended list of genes that are associated with SZ, ASD, DD, and/or SLI, and that are additionally known to play a role in brain rhythmicity and/or are candidates for conditions entailing brain dysrhythmias, like epilepsy. As noted in the introduction, we have chosen these four clinical conditions because of two main reasons. First, we have already improved robust characterizations of their linguistic profile in terms of an abnormal suite of brain rhythms. Second, language impairment in these conditions relate to core aspects of language (and of language processing in the brain), in particular, to the interface between syntax and semantics, and between syntax and phonology.

For SZ we have mostly relied on the Schizophrenia Database (http://www.szdb.org), which currently includes 2689 genes with different levels of evidence: genes resulting from genome-wide analyses (GWA) and copy number variant (CNV)/exome sequencing analyses, genes showing altered methylation patterns in schizophrenics, genes resulting from functional studies or candidate gene approaches, genes with pathogenic single nucleotide polymorphisms (SNPs), and genes found mutated in familial forms of the disease. Within these genes, we have focused on those that have been foundto play a role in language development (and potentially evolution), as discussed in Murphy and Benítez-Burraco (2016). For ASD we have relied mostly on the SFARI database (https://sfari.org), which currently includes 859 genes and ~300 potential candidates for the disorder, based on different levels of evidence (genes bearing rare single variants, disruptions/mutations, or submicroscopic deletions/duplications; candidates resulting from genetic association studies, particularly, GWAs; genes resulting from functional approaches; and genes with CNV associated with ASD).Within these genes, we have equally focused on those highlighted in Benítez-Burraco and Murphy (2016) as important for language development and evolution. For DD, we have relied on the last updated list of candidates for this condition, as provided by Paracchini et al (2016), which includes genes resulting from

candidate association studies and GWAs. Finally, for SLI, we have relied on the literature review provided by Chen et al. (2016) and on the literature survey and results provided by Pettigrew et al (2016).

Our list of potential candidates for these language oscillogenomes is shown in Table 1.

Table 1. The set of candidates comprising the language oscillogenome

	SZ	**ASD**	**Dyslexia**	**SLI**
AUTS2	+			+
CACNA1C	+	+		
CACNA1I	+	+		
CNR1	+	+		
CNTNAP2	+	+		
COL4A2			+	
COMT	+	+		
CX3CR1	+	+		
CYP19A1			+	
DCDC2			+	
DISC1	+	+		
DLX5	+	+		
DLX6	+	+		
DPP10	+	+		
DYRK1A		+		
EGR1	+			
ELP4		+		
ERBB4	+	+		
FMR1	+	+		
FOXP1	+	+		+
GABARAP			+	
GABRB3	+	+		
GAD1	+	+		
GRIN2A	+	+		+
GRIN2B	+	+		+
GRM8	+	+		
HTR1A	+			
KANSL1			+	
KIAA0319			+	
MAPK14	+			
MBD5	+	+		+
MECP2	+	+		
NRG1	+	+		
NSF			+	
PDGFRB	+	+		
PLAUR		+		+
PTEN		+		
ROBO1	+	+	+	
S100B	+		+	
SCN1A		+		
SETBP1		+		+
SHANK3	+	+		

SIRT1	+				
SNAP25	+	+	+		
SRPX2					+
ZNF804A	+	+			

We expected that the 46 genes we highlight here as part of the shared signature of abnormal brain oscillations associated with language deficits are functionally interconnected and map on to specific regulatory pathways, cell types or functions, or aspects of brain development of interest for language and the etiopathogenesis of language impairment in the clinical conditions we have mentioned. Accordingly, we used String 10 (www.string-db.org) for examining potential functional links among the proteins encoded by our candidates. String 10 predicts direct/physical and indirect/functional associations between proteins that derive from four sources: genomic context, high-throughput experiments, conserved coexpression, and the knowledge previously gained from text mining (Szklarczyk et al. 2015). As shown in Figure 1, several proteins (NRG1, ERBB4, PDGFRB, EGR1, MAP14, DISC1, SIRT1, DYRK1A, PLAUR, and SRPX2)are found reciprocally interconnected, hence displayed in the central part of the network. These proteins are indeed involved in different steps of neural development and function, particularly in brain oscillatory activity.

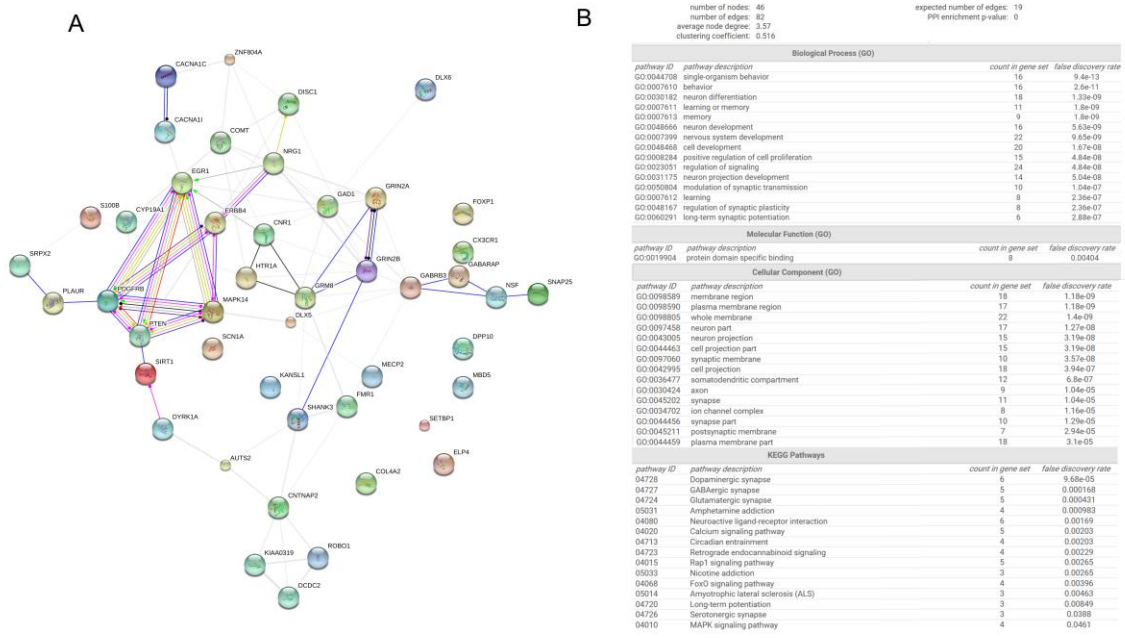

Figure 1. Protein interaction network. The diagram on the left shows the network of known and predicted interactions among proteins encoded by genes proposed as candidates for the language oscillogenome (Table 1). The network was drawn with String (version 10.0; Szklarczyk et al., 2015)) license-free software (http://string-db.org/), using the molecular action visualization. Colored nodes symbolize gene/proteins included in the query (small nodes are for proteins with unknown 3D structure, while large nodes are for those with known structures). The color of the edges represent different kind of known protein-protein associations. Green: activation, red: inhibition, dark blue: binding, light blue: phenotype, dark purple: catalysis, light purple: post-translational modification, black: reaction, yellow: transcriptional regulation. Edges ending in an arrow symbolize positive effects, edges ending in a bar symbolize negative effects, whereas edges ending in a circle symbolize unspecified effects. Grey edges symbolize predicted links based on literature search (co-mentioned in PubMed abstracts). Stronger

associations between proteins are represented by thicker lines. The medium confidence value was .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). 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 (see the main text for details). Functional enrichment of the entire gene set, according to Gene Ontology (GO) consortium annotations, is shown on the right side of the image. This enrichment was performed using String algorithm for gene network analysis. A false-discovery rate cutoff of 0.05, obtained after Bonferroni correction, was set to select significant functions. Except for the "molecular function" annotation, only the top fifteen scoring categories are displayed.

NRG1 contributes to the regulation of neural proliferation in the subventricular zone (Ghashghaei et al. 2006), thalamocortical axon pathfinding (López-Bendito et al. 2006), and glutamatergic and dopaminergic neurotransmission in the thalamus and the striatum (Newell et al. 2013). NRG1 and its receptor ERBB4 regulate as well the migration of GABAergic interneurons from ganglionic eminences to their cortical destinations (Li et al. 2012). Additionally, they play a key role in synchronizing neural oscillations in the cortex. Specifically, they enhance the synchrony of pyramidal neurons via presynaptic interneurons, increase the synchrony between pairs of fast-spiking interneurons and pairs of fast-spiking and non-fast-spiking interneurons in the prefrontal cortex, and enhancekainate-induced gamma oscillations in vivo (Hou et al. 2014). Risk alleles of *NRG1*have been found to correlate with semantic (but not to lexical) verbal fluency in SZ, and with a decreased activation in the left inferior frontal and the right middle temporal gyri as well as the anterior cingulate gyrus of schizophrenic patients (Kircher et al. 2009), but also with reduced left superior temporal gyrus volumes (a robust imaging finding in SZ) (Tosato et al. 2012). Risk polymorphisms of the gene are associated as well with increased IQs, memory, learning performance, and language abilities in subjects with bipolar disorder (Rolstad et al. 2015). Interestingly too, *Nrg1*(+/-) mice exhibit decreased social activity which mimic the social deficits observed in autistic patients (Ehrlichman et al., 2009).

Signalling by NRG1 has been found to increase the expression of an isoform of DISC1, encoded by a robust SZ candidate, during neurodevelopment (Seshadriet al. 2010).DISC1 is involved in neurite outgrowth, cortical development, and callosal formation (Brandon and Sawa 2011; Osbun et al. 2011). θ-induced long-term potentiation is altered in the hippocampal area CA1 of transgenic mice expressing a truncated version of *Disc1* (Booth et al. 2014). Moreover, the inhibitory effect of DISC1 on NRG1-induced ERBB4 activation and signalling also affects the spiking interneuron-pyramidal neuron circuit (Seshadri et al. 2015).

Several other robust candidates for SZ are predicted to be functionally linked to DISC1 and/or NRG1, including CACNA1C, CACNA1I, COMT, and ZNF804A. All of these are known to impact oscillatory patterns. *CACNA1I* and *CACNA1C* encode different subunits of calcium channels. *CACNA1C* encodes the alpha 1C subunit of the Cav1.2 voltage-dependent L-type calcium channel, which contributes to the generation of β and γ waves during wakefulness and REM sleep (Kumar et al. 2015). Risk alleles of the gene correlate with lower performance scores in semantic verbal fluency tasks in schizophrenics (Krug et al. 2010). Pathogenic variants of *CACNA1C* have been identified in subjects with intellectual disability, executive dysfunction, hyperactivity-impulsivity that interferes with Attention-Deficit/Hyperactivity Disorder (ADHD) and/or ASD, as well as forms of childhood-onset epilepsy (Damaj et al. 2015). *CACNA1I* has been related to changes in sleep spindles in schizophrenics, a type of brain rhythm that constrains aspects of the thalamocortical crosstalk, impacting on memory consolidation and learning (Manoach et al. 2015). Likewise, low voltage α has been associated

with low activity levels in COMT (Enoch et al. 2003). Finally, ZNF804A modulates hippocampal γ oscillations and thus, the coordination of hippocampal and prefrontal distributed networks (Cousijn et al. 2015). It also contributes to cortical functioning and neural connectivity, because of its known role in growth cone function and neurite elongation (Hinna et al. 2015). SZ risk polymorphisms of *ZNF804A* result in lower performance scores in reading and spelling tasks (Becker et al. 2012), but also in task evaluating category fluency during semantic processing (Nicodemus et al. 2014). ASNP within intron 2 of the gene has been found to be associated with ASD subjects that are verbally deficient (Anitha et al. 2012).

Concerning *ERBB4*¸ this gene has been related to intellectual disability and speech delay (Kasnauskiene et al. 2013).ERBB4 is predicted to interact with PDGFRB, and putative homologs of these two genes have been found to interact in other species, particularly in *Drosophila melanogaster* and *Caenorhabditis elegans* (Figure 1). In human cells, a direct interaction of PDGFRB and one of the functional isoforms of ERBB4 has been recently documented (Sundwall et al 2010). *PDGFRB* encodes the β subunit of the platelet-derived growth factor (PDGF) receptor, known to be involved in the development of the central nervous system. In mice, the knockout of *Pdgfrb*results in reduced auditory phase-locked *γ* oscillations, which correlates with anatomical, physiological, and behavioural anomalies that are also found in schizophrenics, including reduced density of GABAergic neurons in the amygdala, hippocampus, and medial prefrontal cortex; alterations of prepulse inhibition; reduced social behaviour; impaired spatial memory;and problems with conditioning (Nguyen et al. 2011, Nakamura et al. 2015).

ERBB4 is also a functional partner of PTEN, a phosphatase that preferentially dephosphorylates phosphoinositide substrates. Both proteins collaborate in protrusion formation in rhombic lip cells (Sakakibara and Horwitz, 2006). Functional interactions are predictedas well between PTEN and PDGFRB (Figure 1). *PTEN* is a candidate for a subtype of ASD with macrocephaly whichis usually present in conjunction with epilepsy (or paroxysmal EEG) (Buxbaum et al. 2007; Marchese et al. 2014). The gene is highlighted as a candidate for language deficits in ASD, because patients with PTEN-associated ASD show delayed language development with poor working memory and processing speed (Naqvi et al. 2000, Tilot et al. 2015). PTEN is a major negative regulator of the mTOR signalling pathway, important for synaptic plasticity and neuronal cytoarchitecture (see Tilot et al. 2015 for review). The knockdown of *Pten*in mouse primary neuron cultures affects the expression of genes mapping to pathways associated with neurogenesis, long-term potentiation, and synaptic activity (Lanz et al. 2013).In mice, the deletion of *Pten*in adult hippocampal neural stem cells increases proliferation and differentiation of stem cells toward hypertrophied neurons with abnormal polarity, causes seizures and macrocephaly, and impairs social behaviour (Amiri et al. 2012). Social dysfunction in mouse models of neural *Pten* loss includes repetitive behaviour, impaired emotional learning (in females) and increased anxiety (in males) (Page et al. 2009, Clipperton-Allen and Page 2014), but also seizures and epileptiform features (Ogawa et al. 2007).Interestingly, *Pten* deletion in mice ultimately yields deviant circuit formation in the dentate gyrus, responsible for excitation flow through the hippocampus (Pun et al. 2012), potentially impairing procedural memory capacities relevant to language.

PTEN is a strong partner of MAPK14, which is also functionally related to ERBB4 and PDGFRB (Figure 1). In glioma cells, the downregulation of *MAPK14*correlates with the upregulation of *PTEN*, resulting in the inhibition of cell migration in vitro (Dasari et al. 2010).Mice with a single copy disruption of *Mapk14* show protection against kainite-induced seizures (Namiki et al. 2007). Another partner of PTEN is SIRT1, which regulates

negativelyneurogenesis and neural differentiation, contributes to axon formation and elongation, and plays a role in memory formation (Gao et al. 2010, Li et al. 2013, Saharan et al. 2013). Sirt1 is negatively related to seizures and seizure-induced damage in the hippocampus of rat models of epilepsy via miR activity (Wang et al. 2016). SIRT1 phosphorylation and activation by DYRK1A promotes cell survival (Guo et al. 2010). *DYRK1A*is located within the Down Syndrome Critical Region within chromosome 21. In mice, *Dyrk1a* has proven to contribute to the balance between cortical and thalamic neurons (Guedj et al. 2012). *Dyrk1a* overexpression affects the expression of genes encoding GABAergic and glutamatergic related proteins, shifts the excitation/inhibition balance towards inhibition, and impacts on pathways involved in synaptogenesis and synaptic plasticity (Souchet et al. 2014), supporting a role of this gene in learning and memory (Hämmerle et al. 2003). *DYRK1A* has been related as well to microcephaly, facial dysmorphisms, mental retardation, and absence of speech (Van Bon et al. 2011, Courcet et al. 2012). In mice, the upregulation of *Dyrk1a* also results in the upregulation of *Gad1* (Souchet et al. 2014), which encodes an enzyme that catalyzes the production of GABA, with a specific role in the development of GABAergic neurons in the hippocampus (Pleasure et al. 2000). *GAD1*has been implicated in the pathophysiology of SZ, but also in working memory impairment, because of its impact on prefrontal white matter structure (Lett et al. 2016). Risk alleles of the gene impact as well on long-interval cortical inhibition (LICI) in the dorsolateral prefrontal cortex of schizophrenics, as showed by transcranial magnetic stimulation with electroencephalography (TMS-EEG): this suggests that the gene contributes to GABAergic inhibitory neurotransmission (Lett et al. 2016). Male *Gad1* (+/-) mice exhibit impaired social behavior (Sandhu et al., 2014).

GAD1 interacts with DLX5 and DLX6, two important genes for GABAergic interneuron development (Cobos et al. 2006; Ghanem et al. 2008; Poitras et al. 2010). Accordingly, in the developing ventral forebrain, the non-coding RNA Evf2 controls transcription of *Gad1*, *Dlx5*, and *Dlx6* through trans and cis-acting mechanisms;*Evf2* mouse mutants exhibit reduced synaptic inhibition (Bond et al. 2009). Heterozygous mice for *Dlx5/6* exhibit reduced cognitive flexibility which appears to emerge from abnormal GABAergic interneurons and γ rhythms, particularly in fast-spiking interneurons (Cho et al. 2015), potentially contributing to the irregular long-lasting prefrontal and central γ in ASD, but also to SZ symptoms. Evf2 also recruits Mecp2 to DNA regulatory elements in the Dlx5/6 intergenic region (Bond et al. 2009), whereas *DLX5*has been reported to be modulated by MECP2 (Miyano et al. 2008). *MECP2* is the main candidate for Rett syndrome, a neurodegenerative condition involving autistic behaviour, motor problems, and language loss (Uchino et al. 2001, Veenstra-VanderWeele and Cook 2004). *MECP2* is critical for normal function of GABA-releasing neurons (Chao et al. 2010). In mice, the loss of *Mecp2* from GABAergic interneurons results in auditory event-related potential deficits (Goffinet al. 2014). In response to auditory stimulation,*Mecp2*+/- mice recapitulateselect γ and β band abnormalities and specific latency differences found in ASD subjects (Liao et al. 2012).

Another strong partner of PTEN (but also of MAPK14, PDGFRB, ERBB4, and NRG1) is EGR1, a transcription factor involved in neuronal plasticity and memory consolidation (Veyrac et al. 2014). *EGR1*is found induced in human epileptic foci and its expression levels correlate with the frequency, amplitude, and total area of the interictal spikes, a hallmark of epileptic neocortex (Rakhade et al. 2007). In turn, EGR1 downregulates *PLAUR* (Matsunoshita et al. 2011), which encodes the urokinase plasminogen activator receptor and which is a target of FOXP2, the renowned ‘language gene’ (Roll et al. 2010). Mice lacking *Plaur* have significantly fewer neocortical GABAergic interneurons, which are vital for oscillatory processes (Bae et

al. 2010), and exhibit nearly complete loss in parvalbumin-containing interneurons during brain development, which is associated with increased susceptibility to spontaneous seizures and with impaired social interactions (Bruneau and Szepetowski 2011). PLAUR is an effector of SRPX2, another of FOXP2 targets (Royer-Zemmour et al. 2008) and a candidate for rolandic epilepsy and speech dyspraxia (Roll et al. 2006). One distinctive feature of this benign type of epilepsy with an onset in childhood is the presence of abnormal centrotemporal sharp waves, an endophenotype of rolandic epilepsies that has been associated with *ELP4*(Strug et al. 2009). *ELP4* encodes one component of the elongator protein complex, involved in RNA transcription and tRNA modification, and important for cell mobility and migration, particularly during the development of the cerebralcortex (Creppe et al. 2009). Interestingly, the locus of *ELP4*has been linked to speech sound disorder (SSD) (Pal et al. 2010). Microdeletions of *ELP4* have also been associated with ASD and linguistic deficits (Addis et al. 2015).

EGR1 expression is induced by CNR1 (Bouaboulaet al. 1995). Genomics studies have highlighted *CNR1* as an important gene forbrain changes and metabolic disturbances in SZ (Yu et al. 2013, Suárez-Pinilla et al. 2015), for striatal response to happy faces in a Caucasian cohort of ASD people (Chakrabarti et al., 2006), and for cases of complete absence of expressive speech (Poot et al. 2009). *CNR1* encodes the cannabinoid-1receptor, which modulates θ and γ rhythms in several areas of the brain, including the hippocampus, with an impact on sensory gating function in the limbic circuitry (Hajós et al. 2008). CNR1-positive GABAergic interneurons play an important role in the response to auditory cues, as well as in other aspects of behaviour (Brown et al. 2014).*CNR1*is functionally linked to several other genes encoding a subset of related proteins that also appears as a core component of our network (Figure 1), including *HTR1A*, *GRM8*, *GRIN2A*, *GRIN2B*, and *SHANK3*. Interestingly, most of these genes encode neurotransmitter receptors.

Beginning with *HTR1A*, this encodes the receptor 1A of serotonin and modulates hippocampal γ oscillations, seemingly impacting on behavioural and cognitive functions linked to serotonin function, such as learning and memory (Johnston et al. 2014). *GRIN2A* and *GRIN2B* encode two components of the subunit NR2 of the NMDA receptor channel, involved in long-term potentiation, a physiological process underlying memory and learning. GRIN2A is reduced in fast-firing interneurons of schizophrenics, which play a critical role in γ oscillation formation: a blockade of NR2A-containing receptors increases γ power and reduces low-frequency γ modulation (Kocsis 2012). Mutations in *GRIN2A* cause epilepsy-aphasia spectrum disorders, including Landau-Kleffnersyndrome and continuous spike and waves during slow-wave sleep syndrome (CSWSS), in which language regression and speech impairment are commonly observed (Carvill et al. 2013, Lesca et al. 2013). The gene has been also related to rolandic epilepsies (Dimassi et al. 2014). Speech problems found in patients with mutations in *GRIN2A* include imprecise articulation, problems with pitch and prosody, and poor performance on vowel duration and repetition of monosyllables and trisyllables, which are commonly diagnosed as dysarthria or dyspraxia (Turner et al. 2015).*GRIN2B* plays a key role in normal neuronal development and in learning and memory. Besides its involvement in SZ, ASD, and SLI, mutations in *GRIN2B* have been found in subjects with intellectual disability associated with behavioural problems and EEG anomalies, and in patients with epileptic encephalopathies which co-occur with impairment of motor and cognitive functions (Freunscht et al. 2013, Smigiel et al. 2016, Hu et al. 2016). Finally, *GRM8* encodes a protein with a glutamate, GABA-B-like receptor activity. Several SNPs of the gene have been found associated with θ power in subjects with alcohol dependence, which suggests that variation in *GRM8* may modulate θ rhythms during information processing (Chen et al. 2009).

In several organisms, GRIN2B interacts with SHANK3, a postsynaptic scaffolding protein that seems to be important for the maintenance of the adequate balance between neuronal excitation and inhibition. Knockdown of *Shank3* in mouse primary neuron cultures affects the expression of genes involved in long-term potentiation and synaptic activity (Lanz et al. 2013).Cultured cortical neuron networks lacking *Shank3* show reduced excitation and inhibition behaviours (Lu et al. 2016). Specifically, mice lacking the exon 9 of the gene exhibit reduced excitatory transmission in the hippocampal CA1 region and increased frequency of spontaneous inhibitory synaptic events in pyramidal neurons, which result in mildly impaired spatial memory (Lee et al. 2015). Knocked out mice for the gene exhibit abnormal social interaction and repetitive grooming behaviour (Peça et al. 2011).SHANK3 has been linked as well to some of the distinctive symptoms of Phelan-McDermid syndrome (also known as 22q13 deletion syndrome), including intellectual disability, delayed or absent speech, autistic features, and seizures and abnormal EEG profiles (Soorya et al. 2013, Holder and Quach 2016).

Besides CNVs in *GRIN2A* and *SHANK3*, CNVs in genes related to SLI and DD have been found as well in patients with continuous spike and waves during slow-wave sleep syndrome and Landau-Kleffner syndrome, including *ATP13A4* and *CNTNAP2* (Lesca et al. 2012). The latter encodes a protein associated with K^+ voltage-gated channels in pyramidal cells of the temporal cortex, that are mostly innervated by GABAergic interneurons (Inda et al. 2006). The effect of *CNTNAP2* on language development in the normal population (see Whitehouse et al. 2011, Whalley et al. 2011, Kos et al. 2012) is seemingly due to its role in dendritic arborization and spine development (Anderson et al. 2012), brain connectivity and cerebral morphology (Scott-Van Zeeland et al. 2010, Tan et al. 2010, Dennis et al. 2011). Homozygous mutations or compound heterozygous CNVs of *CNTNAP2* result in epilepsy and language and speech regression (Strauss et al. 2006, Marchese et al. 2016, Smogavec et al. 2016). Interestingly, mice and rats with homozygous deletions of *Cntnap2* show reduced spectral power in the α (9-12 Hz) range during wake (Thomas et al. 2016). In mice, *Cntnap2* is regulated by Auts2 (Oksenberg et al. 2014). *AUTS2* displays the strongest signal of a selective sweep in anatomically-modern humans compared to Neanderthals (Green et al. 2010, Oksenberg et al. 2013) and is a robust candidate for several neurodevelopmental disorders (see Oksenberg and Ahituv 2013 for review) Specifically, CNVs of the gene have been found in patients with language delay and seizures (Nagamani et al. 2013), and the gene has been cited as a candidate for epilepsy (Mefford et al. 2010). Interestingly, *AUTS2* has also been associated with differential processing speeds (Luciano et al. 2011).

As noted above, the dysfunction of GABA signalling contributes to ASD-like stereotypes, Rett syndrome phenotypes, and SZ (Chao et al. 2010, Fazzari et al. 2010). Alteration of the GABA catabolism also results in brain and behavioral anomalies that mimic the symptoms of ASD, including language impairment (Gibson et al. 1997, Pearl et al. 2003).The fact that our list of candidates for the language oscillogenome includes several receptors for GABA reinforces the view that GABA signalling is crucial for the oscillatory signature of language. As shown in Figure 1, a third robust subnetwork includes GABRB3, GABARAP and twointeractors; NSF and SNAP25. *GABRB3* encodes the β-3 subunit of the GABA receptor A (Cook et al. 1998, Shao et al. 2002, Shao et al. 2003). Besides its known association with ASD, the gene has been associated as well with childhood absence epilepsy (Urak et al., 2006).Differences in the expression level of the *GABRB3* have been related to changes in the firing of hippocampal pyramidal neurons and the activity of fast networks (Heisteket al. 2010). More generally, genetic variation in $GABA_A$ receptor properties have been linked to differences in β and γ oscillations, which seemingly impact on network dynamics and cognition (Porjeszet al. 2002). *GABARAP* encodes a $GABA_A$ receptor-associated protein involved in the clustering of

neurotransmitter receptors, but also in inhibitory neural transmission. *Gabarap* knockout mice exhibit abnormal paroxysmal sharp waves in the hippocampus (Nakajima et al. 2012). Estrogen depletion resulting from the inhibition of *CYP19A1* affects GABA synthesis and gives rise to increased spine density and decreased threshold for hippocampal seizures (Zhou et al. 2007). Regarding NSF and SNAP25, both are needed for neurotransmitter release and synaptic function. *NSF* encodes a protein involved in vesicle-mediated transport in the Golgi apparatus, whereas SNAP25 contributes to the formation of the soluble NSF attachment protein receptor complex. In mice, reduced levels of Snap25 seems to be related to more frequent spikes, diffuse network hyperexcitability, and epileptiform discharges, as well as to cognitive deficits and social impairment (Corradini et al. 2014, Braida et al. 2015).

Downregulation of GABA receptors has been linked as well to altered expression of*FMR1*. Specifically, reduced levels of GABRβ3 and of FMRPhave been found in the vermis of adult subjects with ASD (Fatemi et al. 2011), as well as in the hippocampus of *En2*(-/-) mice model of ASD (Provenzano et al. 2015). FMRP is encoded by *FMRP1*, the main candidate for Fragile X syndrome, a condition involving language problems and frequent features of ASD (Kaufmann et al. 2004, Smith et al. 2012). Low levels of FMRP have been found as well in schizophrenic patients with low IQs (Kovács et al. 2013). *Fmr1*knockoutmice exhibit enhanced mGluR5 signalling, which results in altered neocortical rhythmic activity because of changes in neocortical excitatory circuitry (Hays et al. 2011). These mice also exhibit abnormal patterns of coupling between θ and γ oscillations in perisomatic and dendritic hippocampal CA1 local field potentials, resulting in abnormally weak changes during tasks involving cognitive challenge (Radwan et al. 2016). Also, inhibitory dysfunctions in layer II/III of the somatosensory cortex has been found in *Fmr1* knockout mice, in particular, a reduced activation of low-threshold-spiking interneurons and reductions in synchronized synaptic inhibition and coordinated spike synchrony in pyramidal neurons in response to mGluR agonists (Paluszkiewiczet al. 2011).

FMR1 has been suggested to fit with *ROBO1*, *KIAA0319*, *S100B*, and *DCDC2*, among others, into a theoretical molecular network involved in neuronal migration and neurite outgrowth (Poelmans et al. 2011). All these genes are candidates for DDaccording to results from association studies, GWA analyses, and CNVs studies (Paracchini et al. 2016), and all have been related to abnormal patterns of brain oscillations or seizures when mutated. Accordingly, they seem to us to be promising candidates for the oscillatory signature of language. Rare variants in the intergenic region between *DCDC2* and *KIAA0319*, and in one intron of *DCDC2* (*locus* DYX2) have been associated with differences between dyslexic and control children in a late mismatch negativity around 300-700ms originating in right central-parietal areas when discriminating between complex auditory stimuli, such as syllables and words(Czamara et al. 2011). *ROBO1*regulates interaural interaction in auditory pathways (Lamminmäki et al. 2012) and is a target of miR-218, which is significantly downregulated in the hippocampus of patients with medial temporal lobe epilepsy (Kaalund et al. 2014).*S100b* knockout mice show a reduced γ band (30-80 Hz) response in the hippocampus after seizure induction with kainic acid (Sakatani et al. 2007). Altered expressions of *S100B*have been found in patients with medial temporal epilepsy (Lu et al. 2010). This suggests that the S100B-related pathways might contribute to the modulation of brain oscillations in specific conditions. *S100B* encodes a calcium-binding protein involved in neurite extension and axonal proliferation, ultimately being involved in synaptic plasticity and learning.

The remainder of our candidate genes are not clearly functionally interconnected in the core interacting network (Figure 1), although all of them play relevant roles in brain oscillations and

are candidates for the basis of language impairments (see Table 1). This is why we still regard them as important components of the language oscillogenome. *FOXP1*is co-expressed with *FOXP2* in some areas of the brain and the protein FOXP1 forms heterodimers with the FOXP2 protein. *FOXP1*haplo-insufficiencyhas been found in patients with epileptiform discharges, severe speech delay, and delayed gross motor skills (Carr et al. 2010). *Cx3cr1* knockout mice show deficient synaptic pruning, weak synaptic transmission, decreased functional brain connectivity, and social and behavioural features that resemble those found in ASD patients (Zhan et al. 2014). Interestingly, these mice also exhibit reduced θ-driven connections between prefrontal cortex and dorsolateral hippocampus relative to wild-type littermates (Zhan 2015). As with other proteins associated with ion channels, like CNTNAP2, DPP10is of interest due to its binding capacity to K^+ channels and its ability to modify their expression and biophysical properties (Djurovic et al. 2010).Rare mutations in *DPP10* have been associated with ASD (Marshall et al. 2008). *MBD5* encodes a protein with a methyl-CpG-binding domain which binds to methylated DNA. *MBD5* haplo-insufficiency has been associated with epilepsy, severe speech delay, mental retardation, and ASD-features (Williams et al. 2010, Talkowski et al. 2011). *SETBP1* is a candidate for Schinzel-Giedionsyndrome, which entails severe developmental delay and occasional epilepsy (Ko et al. 2013, Miyake et al. 2015). Mutations on the gene also result in social and behavioural problems (Coe et al. 2014). The C-terminal portion of COL4A2 arrests cell proliferation and migration; mutations in *COL4A2* have been found in patients with severe developmental delay and epilepsy (Giorgio et al. 2015, Smigiel et al. 2016).*SCNA1*encodes the large α subunit of the voltage-gated sodium channel NaV1.1, which plays a key role in the generation and propagation of action potentials. Mutations in *SCN1A* have been found in individuals with ASD (Weiss et al. 2003, O'Roak et al. 2011), but mostly in patients with epilepsy (Schutte et al. 2016). In mice, the downregulation of the gene dysregulates hippocampal oscillations and results in a spatial memory deficit (Bender et al. 2013). Finally, *KANSL1* plays a role in chromatin organization and gene transcription regulation as part of the NSL1 complex. *KANSL1* is a candidate for Koolen-de Vrries syndrome, which entails epilepsy, developmental delay, and moderate intellectual disability, mostly impacting expressive language development (Koolen et al. 2016).

The functional enrichment, based on gene ontology (GO) annotations, of our set of candidates for the language oscillogenome (Table 1) points out that most of these genes act in signalling pathways known to be important for language processing via its oscillatory implementation, particularly through dopaminergic, GABAergic and glutamatergic synapses(see GO annotation table in Figure 1). Noticeably, the top-scoring biological processes (resulting from functional annotations) include the regulation of behaviour, learning and memory. Finally, considering the cellular localization of the proteins, most of them appear to localize in the plasma membrane, inside the neuron projection components, confirming their role as regulators of neuronal interconnection.In the next section, we discuss how the role played by these genes may underlie most of the oscillatory aspects of brain function that are important for language production and comprehension.

3. Linking the language oscillogenome to language processing

Having documented the most likely candidates which could constitute a robust oscillogenome, we now turn to the neurocomputational implementation of language processing, and how an abnormal genetic profile can in turn give rise to abnormal oscillatory signatures. The core feature of our oscillogenomic approach is a rich level of cross-disciplinary integration.

As Anderson (2016: 6) says of the relationship between evolutionary psychology and neuroscience, 'function in the brain depends upon, at least: a neural network, an underlying genetic network, and an overlaid chemical gradient. Each of these elements is only partially understood, and their dynamic interactions even less so'. By attempting to draw causal relations between genes, oscillations, and linguistic computations we hope that we can shed some light on the nature of these interactions. As noted earlier, the interpretation and construction of linguistic phrases require a range of particular cross-frequency couplings across certain regions (Murphy 2016a, b). Genes are expected to contribute decisively to the emergence of this global neuronal workspace, yielding specific patterns of long-distance connections among distributed neurons and, as a result, specific oscillatory signatures of language.

Figure 2 details the most recent oscillatory model of linguistic phrase-structure building, which we have elsewhere tested against the abnormal oscillatory profiles documented in ASD and SZ subjects with language deficits (Benítez-Burraco and Murphy, 2016; Murphy and Benítez-Burraco, 2016). In Figure 2, after inhibition reduces over the θ cycle the most excitable representation would be itemized via low-middle γ, followed by other clusters. This complex would then be nested within the phase of left-cortical δ, attributing to the set a phrasal identity. Certain of these γ clusters would then slow to β to be maintained in memory. This process of phrasal construction is assumed in Murphy (2015b) to be the only human-specific linguistic computation. Maintaining mentally constructed visual objects also results in greater fronto-parietal θ synchronisation (Ewerdwalbesloh et al. 2016), suggesting that this frequency band could be optimised for maintaining complex linguistic representations generated in fronto-parietal circuits. In brief, a lexicalisation process generated by a θ-γ code would interact with a phrasal construction process of δ phase-entrainment (see Murphy 2016b for further details). This is a more computationally explicit framework than predictive coding models (e.g. Kesller et al 2016), going beyond simple procedures like 'what' and 'where' computations into set-theoretic notions more in line with contemporary linguistic theory.

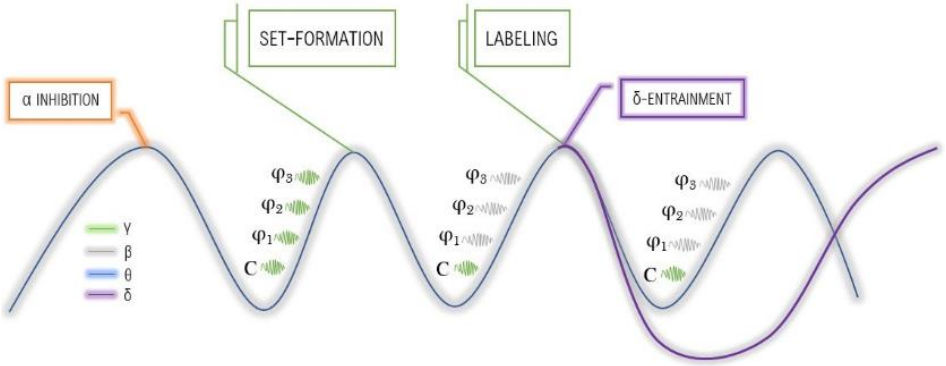

Figure 2. **A multiplexing algorithm for feature-set construction.** 'C' denotes Case feature, 'φ' refers to φ-features (Person, Number, Gender). During the encoding of the feature-set, the initial features are represented at the most preferred phase of θ (the trough), resulting in cross-frequency coupling. Phase-aligned oscillatory activity permits the encoding and decoding of multiple information streams, referred to as multiplexing (Akam and Kullmann, 2014). The hypothesis in Murphy (2016b), adopted here, is that this may be what is required to bind distinct linguistic representations. Reproduced from Murphy (2016b).

Language impairments in ASD at the syntax-semantics interface most often involve difficulties with relative clauses, wh-questions, raising and passives (Perovic and Janke 2013, Perovic et al. 2007, Wada 2015). Both Kikuchi et al. (2013) and Rojas et al. (2008) reported significantly increased γ power for ASD individuals, likely going some way to explain their abnormal linguistic comprehension in tandem with the model in Figure 2, with Kikuchi et al. finding in

addition reduced cross-cortical θ, α and β. Bangel et al. (2014) found reduced β during a number estimation task in ASD, and broader disruptions in rhythmic coordination have been frequently documented. These findings may be (partly) explained through what we have reviewed above; namely, that low voltage α has been associated with low activity levels in COMT (Enoch et al. 2003). As mentioned, *ZNF804A*, *HTR1A* and *GRIN2B*modulate hippocampal γ oscillations (Cousijn et al. 2015) with *ZNF804A* additionally contributing to cortical functioning and neural connectivity, and so these genes may a role in the etiopathogenesis of the ASD γ profile. We also noted that knockout of *Pdgfrb* results in reduced auditory phase-locked γ oscillations, which may be a primary cause of similar oscillatory affects in ASD and SZ. We also reviewed how θ-induced long-term potentiation is altered in hippocampal area CA1 of transgenic mice expressing a truncated version of *Disc1* (Booth et al. 2014).

The ASD oscillome also appears to frequently involve reduced θ during tasks necessitating inter-regional synchronisation (Doesburg et al. 2013). The reduced θ in the ASD population (also documented by Kikuchi et al. 2013) may therefore arise from these or related hippocampal ensembles, which would in turn contribute to working memory deficits, impacting semantic processing.

Unusually long-lasting prefrontal and central γ has also been documented in ASD individuals during the interpretation of semantic incongruity (Braeutigam et al. 2008), possibly indicating the recruitment of a general search mechanism (fast γ) to replace the normal rhythmic processes (slow γ) responsible for retrieving and comparing semantic representations. As noted, heterozygous mice for *Dlx5/6* exhibit reduced cognitive flexibility which appears to emerge from abnormal GABAergic interneurons and γ rhythms (Cho et al. 2015), and it is possible that this is the correct oscillogenomic model to account for this abnormal γ profile.

ASD patients with abnormal levels of *MECP2* show an abnormal γ response in auditory stimulus discrimination tasks (Peters et al. 2015). Similarly, in response to auditory stimulation mice with a heterozygous loss of *Mecp2* function display increased latency of cortically sourced components, and also display γ and β abnormalities associated with ASD and SZ (Liao et al. 2012).Picture-naming tasks also result in reduced γ and β in the left inferior frontal gyrus in ASD participants (Buard et al. 2013), while Jochaut et al. (2015) found altered oscillatory connectivity between auditory and language cortices; results potentially explicable via this oscillogenomic account. In particular, Jochaut et al. discovered that θ-γ coupling is severely impaired during speech processing in ASD (Jochaut et al. 2015), a finding which may relate to the knockout of *Pdgfrb* resulting in reduced auditory phase-locked γ. In addition, we noted that *Fmr1* knockout mice exhibit enhanced mGluR5 signalling, resulting in altered neocortical rhythmic activity (Hays et al. 2011). Since these mice exhibit abnormal patterns of coupling between hippocampal θ and γ (Radwan et al. 2016), this provides another strong oscillogenomic candidate for θ-γ coupling disruptions.

Xu et al.'s (2013) study of lexical decision in SZ also exposed reduced left-temporal and left-frontal α and β – a rhythmic profile also found in Moran and Hong's (2011) and Uhlhaas et al.'s (2008) studies of SZ. Xu et al.'s (2012) sentence presentation task additionally revealed reduced θat occipital and right frontal lobe sites. As noted, the cannabinoid-1 receptor encoded by *CNR1*modulates θ and γ rhythms in several brain areas (Hajós et al. 2008) and so may be involved in these abnormalities. Relatedly, a blockade of NR2A-containing receptors increases γ power and reduces low-frequency γ modulation; we have previously documented unusually fast γ in SZ and ASD patients (Murphy and Benítez-Burraco 2016), and so this may be part of the underling oscillogenomic basis. Decomposing the P300 event-related component into its

constituent θ and δ rhythms, Jones et al. (2004) report significant linkage and linkage disequilibrium between frontal θ band and a single nucleotide polymorphism from the cholinergic muscarinic receptor gene (*CHRM2*) on chromosome 7. Due to the likely role of this gene in higher cognition (Gosso et al. 2007), this makes it a strong candidate gene for cognitive deficits in SZ.

Knockout of *Ppargc1a* in mice decreases the spread of activation in hippocampal CA1 and limits pyramidal cell spiking, giving rise also to unusual modulations of kainate-induced γ oscillations (Bartley et al. 2015). *PPARGC1A* deficiency in ASD may consequently lead to direct oscillatory alterations at this frequency band. We also noted an association between *GRM8* and θ power, suggesting that variations in *GRM8* may modulate θ rhythms during information processing, potentially opening it up as a candidate gene for ASD, SZ and DD, given the abnormal θ modulations documented in these disorders.

With respect to the oscillatory basis of the syntax-phonology interface, we noted that speech problems found in patients with mutations in *GRIN2A* include imprecise articulation and problems with pitch and prosody – archetypal problems documented in DD. Other research indicates that individuals with developmental DD cannot achieve correct phonological representations in the brain, and that these problems arise from impaired phase-locking to slower modulations in the speech signal (below 10Hz, particularly around 2Hz), impacting syllabic parsing (Hämäläinen et al. 2012, see also Lehongre et al. 2011). Due to its relevance in the P300 component, the cholinergic muscarinic receptor gene *CHRM2* is a possible candidate for these δ abnormalities (Callaway 1983). Soltész et al. (2013) observed weaker entrainment in right auditory cortex of dyslexic patients during the processing of tone streams delivered at 2 Hz. The authors suggested a connection between reading performance and neuronal anticipatory phase-synchronization in δ. Abnormal δ rhythms in auditory cortex have been found in dyslexics during the processing of speech sounds too (Molinaro et al. 2016).

It has also been suggested that increased anterior β is a hallmark of dysphonetic dyslexics, who experience problems with grapheme-to-phoneme conversions, whereas increased posterior β are typically found in dyseidetic children, who have difficulties accessing the visual lexicon (Flynn et al. 1992). These findings are compatible with the model in Figure 2, since anterior β is here assumed to be involved in the maintenance of the existing 'cognitive set', with abnormal β impairing the ability of dysphonetic dyslexics to hold one linguistic representation in memory and compare/convert it into another.

Relative to controls, dyslexics also exhibit stronger high γ phase-synchronization in left auditory cortex, possibly indicating the wealth of spectrotemporal information reaching this region, compromising the θ-related auditory buffering capacity along with verbal working memory (Lehongre et al. 2011). This would in turn impair the feature-set combinatorial capacities of dyslexics, with both θ and γ, and their cross-frequency coupling, being abnormal, and so the potential candidate genes discussed above for ASD and SZ (e.g. *GRM8*) are also possible candidates for dyslexia.

Turning to SLI, Bishop et al. (2010) explored the discrimination of non-linguistic sounds in a group of 32 patients, comparing them to syllables in an oddball paradigm. Healthy controls exhibited event-related desynchronization in δ, θ and α during the presentation of oddballs, but SLI patients did not, pointing to a low-level auditory perceptual impairment in SLI. Further studies are needed in order to develop a more fine-grained picture of the perceptual and computational properties of SLI language comprehension, but we can nevertheless conclude

that the candidate genes discussed above for these frequency bands remain potential candidates for the SLI oscillogenome.

Comparing the language deficits observed in dyslexia and SLI on the one hand with those observed in ASD and SZ on the other, it seems clear that they both exhibit δ abnormalities of distinct neurocomputational properties. In dyslexia, entrainment to the speech envelope (phonology) is impaired due to abnormal δ (leading to problems with slow-rate speech processing; Goswami et al. 2013), whereas in ASD and schizophrenia it appears that patients cannot properly exploit the δ-related processes of phrasal construction and identification. The δ rhythm therefore seems to act as a syntax-phonology interface but also a syntax-semantics interface, depending on which other regions are impaired in the particular disorder, such as the right supramarginal gyrus (Cutini et al. 2016) and left inferior frontal gyrus (Molinaro et al. 2016) in dyslexics.

As a way of modelling what we have discussed here, Figure 3 outlines a general schema with some specific examples taken from this section. The bridge between the three levels described here – between the pathophysiology of language deficits in particular cognitive disorders and their linguistic profiles – remains very much open, but we hope that our framework will play a reflective role in theoretically grounding emerging findings in genetics and neural dynamics within a broader understanding of language processing and evolution.

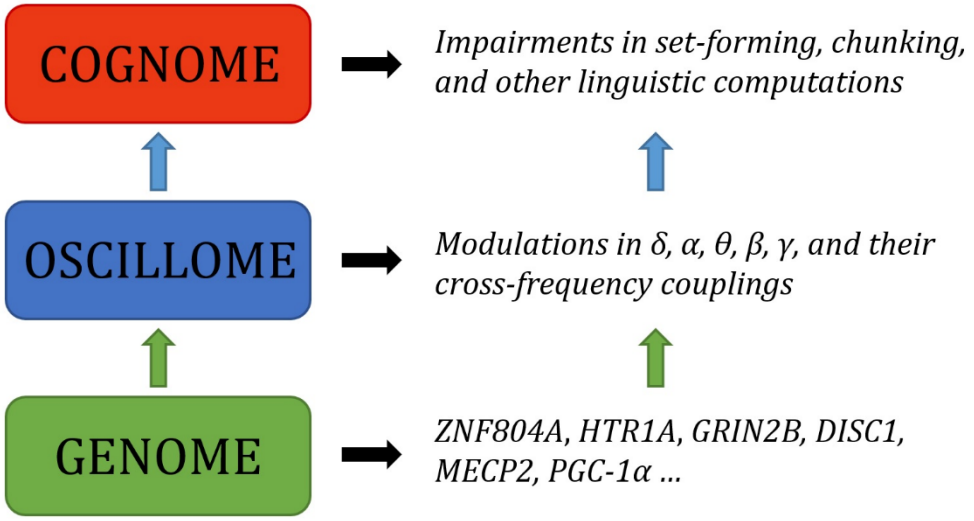

Figure 3. Outline of a putative oscillogenomic model for the human faculty of language. ASD, SZ, SLI and DD have been used as guiding 'oscillopathies', whereas linguistic theory has been employed as a guide for the neurocomputational basis of language. The genome is expected to modulate frequency bands and their interactions at the level of the oscillome, which in turn impacts computational operations at the 'cognome', that is, the basic cognitive operations underlying language, to use a term of Poeppel's (2012).

4. Conclusions

Next generation sequencing technologies have greatly expanded the set of genes associated to cognitive diseases entailing language deficits. In truth, the polygenism seen in these clinical conditions is somewhat commensurable with the polygenism expected for language more generally, which we need to properly seize if we want to understand how language unfolds in the brain and grows in the child. Molecular biology techniques have significantly increased our

knowledge of the role played by these genes in the healthy and the impaired brains. Neuroimaging facilities show how the brain organizes thorough development and processes language, in effect, via the coupling of diverse brain oscillations which enables complex interactions between local and distant brain areas. Nonetheless, it remains imperative to bridge the gap between genes, brain development and function, and language; and consequently to bridge the gap between pathological mutations, abnormal brain activity, and language deficits. Because brain oscillations can provide an explanation for how the brain processes language, but can also construct successful endophentypes of conditions involving language impairment, we have here relied on them to attempt to make substantial theoretical gains in this direction.

Our main conclusion is that the functions of the genes discussed here crucially match aspects of the language oscillome. We have argued that the molecular findings appear to align with the experimental oscillatory results, which in turn align with components of the language cognitive phenotype. As it stands, these findings only afford tenuous causal-explanatory power to the present genome-oscillome-language linking hypotheses, and further experimental oscillatory and genetic research is required to strengthen the viability of the current gene set and increase the number of candidate genes. Specifically, we need to refine the mapping of these and other future candidate genes on specific cell functions, brain areas, aspects of brain function, neuronal developmental processes, and basic cognitive abilities. Animal models will help refine our understanding of the role of these genes and reinforce the links we have highlighted in the paper. Lastly, we expect that our approach will help achieve a better understanding of the complex etiopathogenesis of cognitive conditions entailing problems with language, which should help in turn to design better therapeutic approaches to the diseases (see Wilkinson and Murphy 2016) aimed to ameliorate the symptoms and improve the abilities of the affected people.

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