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The language oscillogenome

Elliot Murphy[1] and Antonio Benítez-Burraco[2]
1. Division of Psychology and Language Sciences, University College London, London, UK
2. Faculty of Philology, University of Huelva, Huelva, Spain

Abstract: Language has been argued to arise, both ontogenetically and phylogenetically, from specific patterns of brain wiring. We argue that it can further 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 propose a set of biologically robust genome-to-language linking hypotheses that, given testing, would 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 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 with prosody and phonology. For a proposal of how to explain these deficits in oscillatory terms, see Benítez-Burraco and Murphy (2016), Murphy and Benítez-Burraco (2016a, b), 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

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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 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 a list of potential candidates. We selected genes that i) are associated with language disorders (DD and SLI) or to language dysfunction in cognitive disorders entailing language deficits (SZ and ASD), and ii) are 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 three main reasons. First, in our previous work (Benítez-Burraco and Murphy 2016, Murphy and Benítez-Burraco 2016a,b, Jiménez-Bravo et al. 2017), we have provided characterizations of their linguistic profile in terms of an abnormal suite of brain rhythms and we have advanced some promising gene-oscillations-language links. 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. Third, we have already proposed a list of candidate genes for the oscillopathic profile of language dysfunction in these conditions.

For SZ we have mostly relied on the Schizophrenia Database (SZDB) (http://www.szdb.org). We have considered 679 candidates based on different source of evidence: candidates resulting from genome-wide association studies (GWAs), genes affected by copy number variant (CNV), genes identified by convergent functional genomics, and genes identified by linkage and association studies. Within these genes, we have identified those that have been found to play a role in language development (and potentially evolution), and to play as well some known role in brain rhythmicity, as discussed in Murphy and Benítez-Burraco (2016a) and Murphy and Benítez-Burraco (2016b). For ASD we have relied mostly on the SFARI database (https://sfari.org), which currently includes 881 genes related to the disorder, based on different levels of evidence (genes bearing rare single variants, disruptions/mutations, or small

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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) and Murphy and Benítez-Burraco (2016b) as important for language development and evolution. For DD, we have mostly 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, GWAs, quantitative GWAs, CNV studies, and next-generation sequencing (NGS) analyses, although we have also surveyed the literature looking for additional candidates. As before, we selected among these genes those with a known role in brain oscillations. Finally, for SLI, we have mostly relied on the literature review provided by Chen et al. (2017) and on the literature survey and results provided by Pettigrew et al (2016), which contain candidates resulting from linkage analyses, GWA studies, and NGS analyses. As with DD, we surveyed the literature looking for other candidates for this condition. Among these genes, we selected, as noted, those with a stablished role in brain rhythmicity.

Our list of potential candidates for the language oscillogenome is shown in Table 1.

	SZ	**ASD**	**Dyslexia**	**SLI**	**Oscillomic/oscillopathic features**
AKT1	+				θ, α, β, γ
APOE	+				θ, α, δ
AUTS2	+			+	Epilepsy
CACNA1C	+	+			β, γ
CACNA1I	+	+			Sleep spindles
CNR1	+	+			θ, γ
CNTNAP2	+	+			α
COL4A2			+		Epilepsy
COMT	+	+			α
CX3CR1	+	+			θ
CYP19A1			+		Seizures
DCDC2			+		MMN 300-700 ms
DISC1	+	+			θ
DLX5	+	+			γ
DLX6	+	+			γ
DPP10	+	+			K^+ channels
DYRK1A		+			Inhibition of neural activity
EGR1	+				Epilepsy
ELP4		+			High amplitude centrotemporal sharp waves
ERBB4	+	+			γ
FMR1	+	+			θ, γ
FOXP1	+	+		+	Epileptiform discharges
GABARAP			+		β, γ, paroxysmal sharp waves
GABRB3	+	+			β, γ, paroxysmal sharp waves
GAD1	+	+			Long-interval cortical inhibition
GRIN2A	+	+		+	γ
GRIN2B	+	+		+	EEG anomalies

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GRM8	+	+			θ
HTR1A	+				γ
KANSL1			+		Epilepsy
KIAA0319			+		MMN 300-700 ms
MAPK14	+				Kainate-induced seizures
MBD5	+	+		+	Epilepsy
MECP2	+	+			γ , β
NRG1	+	+			γ
NSF			+		Epilepsy
PDGFRB	+	+			γ
PLAUR		+		+	Seizures
PTEN		+			Epilepsy, paroxysmal EEG
ROBO1	+	+	+		Epilepsy
S100B	+		+		γ
SCN1A		+			Epilepsy
SETBP1		+		+	Epilepsy
SHANK3	+	+			Seizures, abnormal EEG
SIRT1	+				Seizures
SNAP25	+	+	+		Epilepsy
SRPX2				+	Centrotemporal sharp waves
ZNF804A	+	+			γ

Table 1. The set of candidates comprising the language oscillogenome. The genes shadowed in grey are those found strongly interconnected in our network, as shown in Figure 1 and discussed in the text.

We expected that the 48 genes we highlight here as part of the shared signature of abnormal brain oscillations associated with language deficits exhibit some kind of functional relationship, and map on to particular regulatory pathways, cell types or functions, or facets of brain development and function of relevance for language and the etiopathogenesis of language impairment in the clinical conditions we have mentioned. Accordingly, we used String 10.5 (www.string-db.org) for examining potential functional links among the proteins encoded by our candidates. String 10 is a predictive tool of direct/physical and indirect/functional associations between proteins that are derived from four sources: genomic context, high-throughput experiments, conserved coexpression, and the knowledge previously gained from text mining (Szklarczyk et al. 2015). In order to uncover potential clusters within our network, a MCL clustering algorithm (inflation parameter = 2) was applied to the distance matrix obtained from the String global scores. The MCL algorithm was used because it is remarkably robust to graph alterations and provides with better extractions of complexes from interaction networks (Brohée and van Helden 2006). As shown in Figure 1, our network comprises several clusters of interest. Also, several proteins (NRG1, ERBB4, PDGFRB, EGR1, APOE, AKT1, MAPK14, PTEN, DISC1, SIRT1, PLAUR, SRPX2, and S100B) are found strongly interconnected: they belong to the same cluster and the confidence values of most of the edges are high (0.700) or at the highest (0.900). Hence, we expect them to be key, core components of the regulatory network involved in different steps of neural development and function important for language processing, particularly in brain oscillatory activity.

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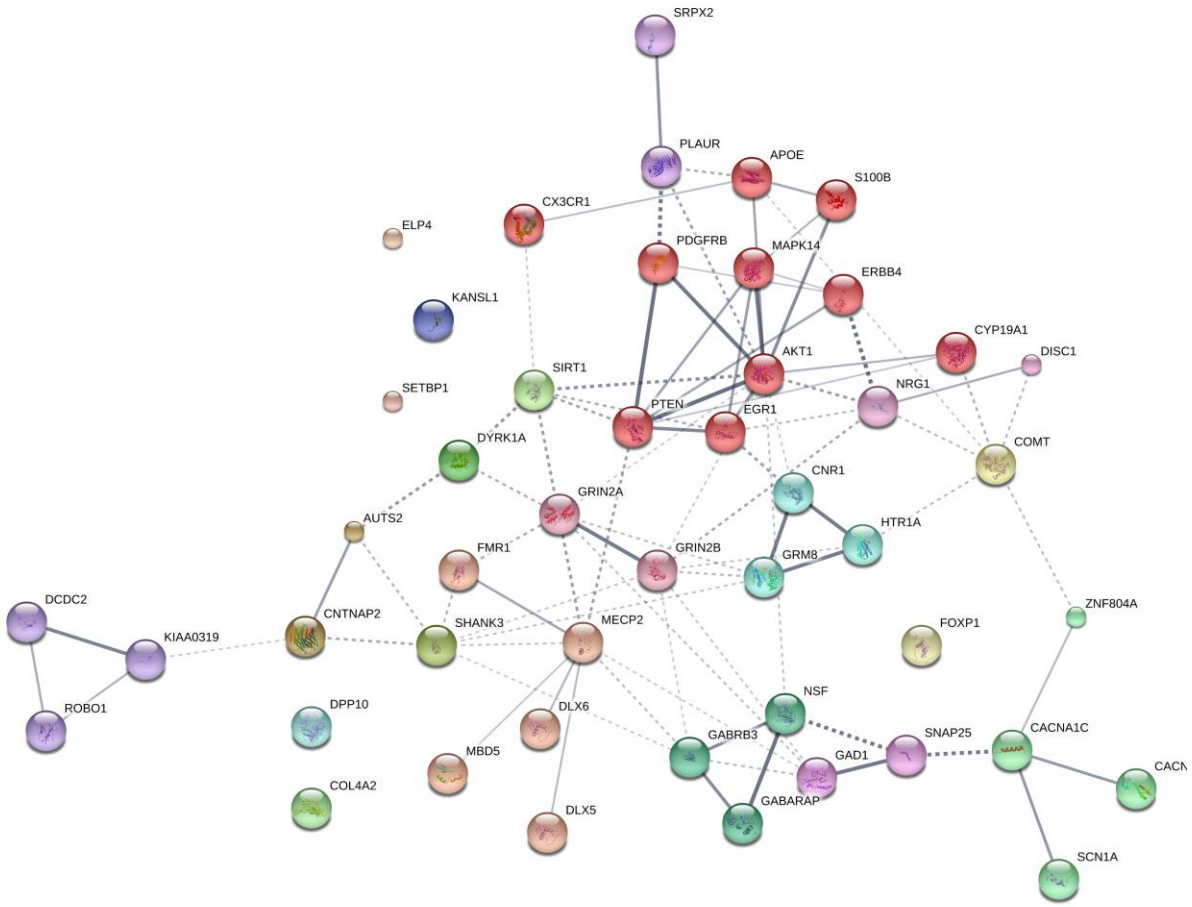

Figure 1. Protein interaction network. The diagram shows the network of known and predicted interactions among proteins encoded by genes proposed as candidates for the language oscillogenome (Table 1). The network was drawn with String (version 10.0; Szklarczyk et al., 2015) license-free software (http://string-db.org/), using the confidence visualization. It contains 48 nodes and 86 edges, with an average node degree of 3.58 and an average local clustering coefficient of 0.384. Colored nodes symbolize proteins included in the query (small nodes are for proteins with unknown 3D structure, while large nodes are for those with known structures). The line thickness of the edges indicates the strength of data support. 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). Each protein cluster is represented with a different color of the nodes. Inter-cluster edges are represented by dashed-lines. 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 and Table 2 for a GO analysis).

NRG1 is a membrane glycoprotein that mediates cell-cell signaling and that 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 how GABAergic interneurons migrate from ganglionic eminences to cortex (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

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presynaptic interneurons, increase the synchrony between pairs of fast-spiking interneurons and non-fast-spiking interneurons in prefrontal cortex, and enhance kainate-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 right middle temporal gyri and the anterior cingulate gyrus, as well as the left inferior frontal of schizophrenic patients (Kircher et al. 2009), but also with a reduction of the left superior temporal gyrus volumes (Tosato et al. 2012). Risk polymorphisms of the gene are also implicated in enhanced memory, IQ scores and linguistic abilities in patients 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).

Epistatic interactions between *Nrg1* and *Akt1* have been found to regulate aspects of behavioral phenotypes and social functions in genetic mouse models of SZ; specifically, double mutant mice exhibit impaired episodic-like memory and impaired sociability, as well as reduced ultrasonic vocalization calls (Huang et al 2015). Likewise, epistatic interactions between SZ-risk polymorphisms of *AKT1* and *COMT* (discussed below) are relevant for human medial temporal lobe structure and memory function (Tan et al. 2012a). Functional polymorphisms of *AKT1* have been related to the dopaminergic signalling in the prefrontal-striatal circuits responsible for the manipulative component of the working memory (Tan et al, 2012b). Specifically, an *AKT1* allele has been associated with verbal learning and memory (Pietiläinen et al. 2009). Genetic deletion of *Akt1* in mice impairs hippocampal long-term potentiation and affects spatial learning, suggesting that *AKT1* contributes to regulate hippocampal neuroplasticity and cognition (Balu et al. 2012). Specifically, female *Akt1*(-/-) mice exhibit increased hippocampal oscillation power in the theta, alpha, beta, and gamma frequency ranges (Chang et al. 2016). AKT1 also regulates GABAergic neuron differentiation and GABAAR expression, important for hippocampus-dependent cognitive functions (Chang et al. 2016). AKT1 interacts with S100B to promote neuronal cell proliferation (Arcuri et al. 2005). *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). Subjects with medial temporal epilepsy show altered expressions of *S100B* (Lu et al. 2010). Overall, this is suggestive of some role for S100B-related pathways in 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. Phosphorylation of Akt is enhanced by APOE (specifically, APOE3) (Okoro et al. 2016), whereas APOE interacts with S100B during astrocytic activation/inhibition ((Mori et al. 2005). *APOE* encodes a component of the Reelin signalling pathway, which has been involved in verbal memory deficits in SZ (Verbrugghe et al. 2012; Li et al. 2015). *APOE* is the most significant genetic risk factor for late-onset Alzheimer Disease (and thus, for the progressive decline in memory, executive function, and language, observed in this condition (Huynh et al. 2017). It has been suggested that *APOE* is also a candidate for primary progressive aphasia (see Rogalski et al. 2013 for discussion). Interestingly, *APOE* has been related to some of the metabolic changes that allowed bigger brains (and eventually, enhanced cognitive capacities) to emerge in our clade (Bufill and Carbonell, 2006). Interestingly too, the allele ε4 of the gene (consistently related to a higher risk for developing late onset Alzheimer's disease) differentially affects low and high frequency bands (particularly, alpha, theta and delta) in several areas of the brain, plausibly accounting for the reduced cognitive abilities of the carriers (Canuet et al. 2012, Cuesta et al. 2015, Liang et al. 2017)

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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, a protein containing multiple coiled coil motifs and located in the nucleus, cytoplasm and mitochondria, is involved in cortical development, callosal formation, and neurite outgrowth (Brandon and Sawa 2011; Osbun et al. 2011). *DISC1* has been associated to verbal reasoning in the general population (Thomson et al., 2014) and to category fluency in people with bipolar disorder (Palo et al., 2007) and schizophrenia (Nicodemus et al. 2014). Importantly, *DISC1* is regulated by FOXP2, a transcription factor encoded by the 'language gene' par excellence (Walker et al. 2012). 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 affects the interneuron-pyramidal neuron circuit (Seshadri et al. 2015).

Several other 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 β and γ wave generation (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 form of oscillation that constrains aspects of 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, a catechol-O-methyltransferase that catalyzes the O-methylation of neurotransmitters like dopamine, epinephrine, and norepinephrine (Enoch et al. 2003). *COMT* has been regularly associated with language performance and processing, and language acquisition, particularly with verbal fluency (Krug et al. 2009, Soeiro-De-Souza et al. 2013, Sugiura et al. 2017), but also with reading abilities (Landi et al. 2013). Finally, ZNF804A, a zinc finger binding protein, 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, which plays an important role in central nervous system development. In mice, the knockout of *Pdgfrb* results in reduced auditory phase-locked γ, which correlates with anatomical, physiological, and behavioural anomalies that are also found in schizophrenics, including decreased GABAergic compactness in the medial prefrontal

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cortex, the hippocampus, and the amygdala, deficient spatial memory and impaired social behaviour (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 predicted as well between PTEN and PDGFRB (Figure 1). *PTEN* is a candidate for a subtype of ASD with macrocephaly which is 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 a delay in language development, characterised by poor processing speed and working memory (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 involved in neurogenesis, synaptic activity, and long-term potentiation (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, a p38 mitogen-activated protein kinase 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). The inhibition of MAPK14 activity suppresses hippocampal-dependent associative and spatial memory deficits in mouse models of synaptic dysfunction (Roy et al. 2015). Mice with a single copy disruption of *Mapk14* show protection against kainate-induced seizures (Namiki et al. 2007). Another partner of PTEN is SIRT1, a deacetylase of the sirtuin family, which negatively regulates neurogenesis 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 prevents seizures and seizure-induced damage in the hippocampus of rat models of epilepsy via miR activity (Wang et al. 2016). The gene is also highly expressed in the cochlea and the auditory cortex (Xiong et al. 2014). SIRT1 phosphorylation and activation by DYRK1A, a dual-specificity tyrosine phosphorylation-regulated kinase, 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 lack of speech, mental retardation and microcephaly (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 a glutamic acid decarboxylase 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 related to the pathophysiology of SZ, but

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also to working memory deficits, because of its impact on prefrontal white matter structure (Lett et al. 2016). GAD1 is a target of FOXP2 (Konopka et al. 2009). 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 genes that encode homeobox transcription factors important 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 cis- and trans-acting mechanisms; *Evf2* mouse mutants exhibit reduced synaptic inhibition (Bond et al. 2009). *Dlx5* and *Foxp2* are expressed in the same intercalated cell masses of the amygdala in non-human primates and in rats, and in nearly the same neuronal populations of the striatum (Kaoru et al., 2010). *DLX5* and *DLX6* are core components of the gene network accounting for aspects of the evolution of our ability to learn and uses languages (see Boeck and Benítez-Burraco 2014 for review). 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 principal candidate for Rett syndrome, a neurodegenerative disease involving autistic behaviour, motor problems, and language loss (Uchino et al. 2001, Veenstra-VanderWeele and Cook 2004). MECP2 is a chromosomal protein that binds to methylated DNA and mediates transcriptional repression, and that is critically needed 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 recapitulate select 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 that contributes to neural 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 area of the interictal spikes, a hallmark of epileptic neocortex (Rakhade et al. 2007). *EGR1* is a target of FOXP2 (Konopka et al. 2009). In turn, EGR1 downregulates *PLAUR* (Matsunoshita et al. 2011), which encodes the urokinase plasminogen activator receptor and which is also a target of FOXP2 (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, a protein with three sushi repeats motifs which is 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

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development of the cerebral cortex (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 for brain anomalies and metabolic changes 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 total absence of expressive speech (Poot et al. 2009). *CNR1* encodes the cannabinoid-1 receptor, which modulates θ and γ rhythms in different brain areas, such as 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 contributes to the modulation of hippocampal γ, influencing cognitive functions linked to serotonin, such as learning and memory (Johnston et al. 2014). Interestingly, the serotonin-1A receptor exhibits a lateralized distribution in the language areas, being the receptor binding 1.8-2.9% higher in right language areas and 2-3.6% higher in left auditory regions (Fink et al. 2009). *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 contribute decisively to γ oscillation formation: a blockade of NR2A-containing receptors increases γ power and reduces the modulation of γ by low frequencies (Kocsis 2012). Language regression and speech impairments have also been found to result from *GRIN2A* mutations (Carvill et al. 2013, Lesca et al. 2013). The gene is also a candidate for rolandic epilepsies (Dimassi et al. 2014). Speech problems found in patients with mutations in *GRIN2A* include imprecise articulation, problems with pitch and prosody, and low 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. Partial duplications of the gene have been associated to developmental delay and intellectual disability (DECIPHER patients 338209 and 289333). Several SNPs of the *GRM8* 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

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(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 largely innervated by GABAergic interneurons (Inda et al. 2006). *CNTNAP2* additionally affects language development in non-pathological populations (see Whitehouse et al. 2011, Whalley et al. 2011, Kos et al. 2012). This effect is seemingly due to its role in dendritic arborization and spine development (Anderson et al. 2012), and in the regulation of cerebral morphology and brain connectivity (Scott-Van Zeeland et al. 2010, Tan et al. 2010, Dennis et al. 2011). Homozygous mutations or compound heterozygous CNVs of *CNTNAP2* are associated with speech and language regression and epilepsy (Strauss et al. 2006, Marchese et al. 2016, Smogavec et al. 2016). Interestingly, mice and rats with homozygous deletions of *Cntnap2* exhibit reduced spectral power in the α (9-12 Hz) range during wake (Thomas et al. 2016). In mice, *Cntnap2* is regulated by Auts2, a protein with a suggested role in cytoskeletal regulation (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 strong 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). Abnormal changes in the GABA catabolism give rise to brain and behavioral disturbances that recapitulate 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 subnetwork includes GABRB3, GABARAP and two interactors; 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). Null mutations of *Gabrb3* in mice result in cleft palate and epilepsy (Homanics et al. 1997), whereas heterozygous deletion also encompassing Ube3a and Atp10a, recapitulates Angelman syndrome, a neurobehavioral disorder involving absence of language (Jiang et al. 2010). 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* is a candidate for dyslexia and encodes a $GABA_A$ receptor-associated protein involved in the clustering of neurotransmitter receptors, but also in inhibitory neural

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transmission. *Gabarap* knockout mice exhibit abnormal paroxysmal sharp waves in the hippocampus (Nakajima et al. 2012). Estrogen depletion resulting from the inhibition of the dyslexia candidate *CYP19A1*, a member of the cytochrome P450 family that catalyzes the formation of aromatic C_{18} estrogens from C_{19} androgens, affects GABA synthesis and gives rise to increased spine density and decreased threshold for hippocampal seizures (Zhou et al. 2007). Regarding NSF and SNAP25 (the former a candidate for dyslexia and the latter a candidate for SZ, ASD, and dyslexia), 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 FMRP have 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, a polyribosome-associated RNA-binding protein, is encoded by *FMRP1*, the main candidate for Fragile X syndrome, a condition involving language deficits 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*-knockout mice 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 gene network important for neurite outgrowth and neuronal migration (Poelmans et al. 2011). All these genes are candidates for DD according 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*, which encodes a doublecortin domain-containing protein (*locus* DYX2) have been associated with differences between dyslexic and control children in a late mismatch negativity around 300-700 ms originating in right central-parietal areas when discriminating between complex auditory stimuli, such as syllables and words (Czamara et al. 2011). The protein encoded by *ROBO1* is a membrane receptor of the immunoglobulin superfamily which contributes to regulate interaural interaction in auditory pathways (Lamminmäki et al. 2012). *ROBO1* is targeted by miR-218, which is found downregulated in the hippocampus of people suffering from medial temporal lobe epilepsy (Kaalund et al. 2014).

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*, which encodes a

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forkhead box transcription factor, is co-expressed with *FOXP2* in some areas of the brain and the protein FOXP1 forms heterodimers with the FOXP2 protein. *FOXP1* haplo-insufficiency has 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). *CX3CR1* encodes a receptor for fractalkine, a chemokine and transmembrane protein important for cell adhesion and migration. Specifically, CX3CR1 has been involved in the crosstalk between the microglia and the neural stem/progenitor cells during adult hippocampal neurogenesis, which is important for memory, learning and cognition (de Miranda et al. 2017), to the extent that CX3CR1 deficiency results in impairment of hippocampal cognitive function and synaptic plasticity (Rogers et al. 2011). As with other proteins associated with ion channels, like CNTNAP2, DPP10 is 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). Interestingly, the transcription start site of the gene is hypermethylated in the neurons of the prefrontal cortex of humans compared to extant primates, and regulatory sequences at *DPP10* carry elevated nucleotide substitution rates and regulatory motifs absent in archaic hominins, with signals of recent selective pressures and adaptive fixations in modern populations (Shulha et al. 2012). This reinforces the view that this gene might have contributed to cognitive abilities and disorders that are unique to humans *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). The gene encodes a methyl-CpG-binding protein. *SETBP1*, which encodes a SET binding protein, is a candidate for Schinzel-Giedion syndrome, 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). As a candidate for SLI, GWAs studies have associated *SETBP1* to the complexity of linguistic output (Kornilov et al. 2016). Microdeletions causing the disruption of the gene impact mostly on expressive abilities, whereas receptive language is quite preserved, to the extent that some patients are able to communicate using gestures and mimics (Filges et al. 2011, Marseglia et al. 2012). The C-terminal portion of COL4A2 arrests cell proliferation and migration; mutations in DD-candidate *COL4A2* have been found in patients suffering from epilepsy and severe developmental delay (Giorgio et al. 2015, Smigiel et al. 2016). *SCN1A* 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 people with ASD (Weiss et al. 2003, O'Roak et al. 2011), but mostly in patients with epilepsy (Schutte et al. 2016). The gene is also associated with Dravet syndrome, a condition characterised by cerebellar signs and a deficit in expressive language with relatively spared comprehension, resulting from motor speech problems which affect to motor planning and executing (Battaglia et al. 2013, Turner et al. 2017). In mice, the downregulation of *Scn1a* disturbs hippocampal oscillations and impairs spatial memory (Bender et al. 2013). Finally, *KANSL1*, which encodes a putative transcriptional regulator involved in the acetylation of nucleosomal histone H4, plays a role in gene transcription regulation and chromatin organization as part of the NSL1 complex. *KANSL1* is a candidate for Koolen-de Vrries syndrome, which entails epilepsy and developmental delay with moderate intellectual disability, which impacts mostly on expressive language abilities (Koolen et al. 2016).

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The functional enrichment, based on gene ontology (GO) annotations performed using String algorithm, of our set of candidates for the language oscillogenome (Table 2) points out that most of these genes act in signalling pathways found to be of significance for language processing via its oscillatory implementation, particularly through dopaminergic, GABAergic and glutamatergic synapses (see Boeckx and Benítez-Burraco 2014a, b for discussion). The top-scoring biological processes (resulting from functional annotations) include the regulation of cognitive process of particular relevance for language, including learning and memory. Lastly, regarding the cellular localization of the proteins, the majority of them seem to be found 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.

Biological Process (GO)			
pathway ID	*pathway description*	*count in gene set*	*false discovery rate*
GO:0044708	single-organism behavior	16	2.07e-12
GO:0007610	behavior	16	5.66e-11
GO:0030182	neuron differentiation	19	2.25e-10
GO:0048468	cell development	22	9.17e-10
GO:0048666	neuron development	17	1.16e-09
GO:0007611	learning or memory	11	2.03e-09
GO:0007613	memory	9	2.03e-09
GO:0007399	nervous system development	23	2.69e-09
GO:0023051	regulation of signaling	26	2.69e-09
GO:0008284	positive regulation of cell proliferation	16	6.28e-09
GO:0031175	neuron projection development	15	6.28e-09
GO:0050804	modulation of synaptic transmission	11	6.28e-09
GO:0048167	regulation of synaptic plasticity	9	8.92e-09
GO:0030030	cell projection organization	17	8.99e-09
GO:0048699	generation of neurons	19	8.99e-09
Molecular Function (GO)			
pathway ID	*pathway description*	*count in gene set*	*false discovery rate*
GO:0048156	tau protein binding	3	0.000993
GO:0019904	protein domain specific binding	8	0.00284
GO:0005102	receptor binding	11	0.0299
GO:0008066	glutamate receptor activity	3	0.0351
Cellular Component (GO)			
pathway ID	*pathway description*	*count in gene set*	*false discovery rate*
GO:0098589	membrane region	18	2.79e-09
GO:0098590	plasma membrane region	17	2.79e-09
GO:0097458	neuron part	18	3.09e-09
GO:0098805	whole membrane	22	3.09e-09
GO:0043005	neuron projection	16	5.2e-09
GO:0044463	cell projection part	16	5.2e-09
GO:0042995	cell projection	20	1.46e-08
GO:0097060	synaptic membrane	10	4.91e-08
GO:0036477	somatodendritic compartment	13	9.06e-08
GO:0044297	cell body	10	9.05e-06
GO:0030424	axon	9	1.43e-05
GO:0045202	synapse	11	1.43e-05
GO:0034702	ion channel complex	8	1.52e-05
GO:0044456	synapse part	10	1.85e-05
GO:0030425	dendrite	9	3.65e-05

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KEGG Pathways			
pathway ID	*pathway description*	*count in gene set*	*false discovery rate*
04728	Dopaminergic synapse	7	4.36e-06
04727	GABAergic synapse	5	0.000209
04015	Rap1 signaling pathway	6	0.000513
04068	FoxO signaling pathway	5	0.000513
04724	Glutamatergic synapse	5	0.000513
05031	Amphetamine addiction	4	0.000778
04080	Neuroactive ligand-receptor interaction	6	0.00155
04020	Calcium signaling pathway	5	0.00187
04713	Circadian entrainment	4	0.00187
04723	Retrograde endocannabinoid signaling	4	0.00217
05033	Nicotine addiction	3	0.00272
05014	Amyotrophic lateral sclerosis (ALS)	3	0.00526
04010	MAPK signaling pathway	5	0.00657
05214	Glioma	3	0.00813
04720	Long-term potentiation	3	0.00834

Table 2. Functional enrichment of the entire set of candidates for the oscillogenome. according to Gene Ontology (GO) consortium annotations. 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.

In other to check the language-specificity of our network, we compared the functional annotations of our network with the result of the functional enrichment analyses of the whole set of candidates for the four conditions also considered in our work (SZ, ASD, DD and SLI). Because the String algorithm did not provide with significant results for DD and SLI, we instead relied on Enrichr (http://amp.pharm.mssm.edu/Enrichr/). The results are shown in table 3.

[TABLE 3 ABOUT HERE]

Biological Process (GO)				
Language oscillogenome	*SZ*	*ASD*	*DD*	*SLI*
single-organism behavior	synaptic transmission	behavior	neuron migration	learning
behavior	regulation of synaptic transmission	single-organism behavior	cell migration involved in sprouting angiogenesis	single-organism behavior
learning or memory	behavior	cognition	neuron recognition	learning or memory
cognition	single-organism behavior	regulation of synaptic transmission	histone H4-K8 acetylation	cognition
regulation of synaptic transmission	cognition	synaptic transmission	chondrocyte development	neuron recognition
Molecular Function (GO)				

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Language oscillogenome	*SZ*	*ASD*	*DD*	*SLI*
tau protein binding	extracellular ligand-gated ion channel activity	gated channel activity	estrogen receptor binding	N-methyl-D-aspartate selective glutamate receptor activity
glutamate receptor activity	glutamate receptor activity	ion channel activity	arginine N-methyltransferase activity	axon guidance receptor activity
gated channel activity	excitatory extracellular ligand-gated ion channel activity	passive transmembrane transporter activity	steroid hormone receptor binding	LRR domain binding
calcium channel activity	ligand-gated ion channel activity	channel activity	PDZ domain binding	ionotropic glutamate receptor activity
protein serine/threonine/tyrosine kinase activity	ligand-gated channel activity	substrate-specific channel activity	histone-arginine N-methyltransferase activity	extracellular-glutamate-gated ion channel activity
Cellular Component (GO)				
Language oscillogenome	*SZ*	*ASD*	*DD*	*SLI*
synapse part	synapse part	synapse part	axolemma	axolemma
synaptic membrane	synaptic membrane	synaptic membrane	neuron projection membrane	neuron projection membrane
ion channel complex	postsynaptic membrane	postsynaptic membrane	cell body	cell surface
postsynaptic density	integral component of plasma membrane	integral component of plasma membrane	centriole	N-methyl-D-aspartate selective glutamate receptor complex
transporter complex	dendrite	transmembrane transporter complex	neuronal cell body	synaptic membrane
KEGG Pathways				
Language oscillogenome	*SZ*	*ASD*	*DD*	*SLI*
Dopaminergic synapse	Neuroactive ligand-receptor interaction	Calcium signaling pathway	Rap1 signaling pathway	Rap1 signaling pathway
GABAergic synapse	Dopaminergic synapse	Neuroactive ligand-receptor interaction	PI3K-Akt signaling pathway	Nicotine addiction

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Glutamatergic synapse	Nicotine addiction	Glutamatergic synapse	GABAergic synapse	Cocaine addiction
Rap1 signaling pathway	Amphetamine addiction	Serotonergic synapse	Ovarian steroidogenesis	Axon guidance
FoxO signaling pathway	Cocaine addiction	Retrograde endocannabinoid signaling	Vasopressin-regulated water reabsorption	Amyotrophic lateral sclerosis (ALS)

Table 3. Comparison of the functional enrichment of candidates for the oscillogenome. SZ, ASD, DD, and SLI. This enrichment was performed using the Enrichr algorithm for gene network analysis. A false-discovery rate cutoff of 0.05, obtained after Fisher exact test correction, was set to select significant functions. Only the top five scoring categories are displayed. Categories are ranked according to their adjusted p value, which derives from running the Fisher exact test for many random gene sets in order to compute a mean rank and standard deviation from the expected rank for each term in the gene-set library and finally calculating a z-score to assess the deviation from the expected rank.

As expected, the top-scoring biological processes resulting from the GO analyses are quite similar across groups, supporting the view that although learning and memory are key aspects of language acquisition and processing, their impairment can result in different cognitive disorders. Regarding the cellular components in which our candidates for the language oscillogenome are preferably found, they are specifically involved in ion channel formation and function, contrary to candidates for SZ, ASD, DD, or SLI, reinforcing the view that our candidates are important for aspects of brain rhythmicity. That said, we believe that the language-specificity of our oscillogenomic candidates might rely on the pathways to which they contribute. Specifically, they are components of the dopaminergic signalling pathway, which is usually highlighted as important for motor behaviour and vocal learning (Kameda et al. 2011). More importantly, they contribute as well to GABAergic signalling, which is relevant for the maintenance of our species-specific cognitive profile (Long et al. 2013). As discussed in detail in Boeckx and Benítez-Burraco (2014a), some of the key changes that contributed to the emergence of our ability to learn and use languages (usually referred to as our language-readiness) involved GABAergic signalling. Among them we wish highlight the evolutionary changes in the core candidate for globularization of the human skull/brain, namely, *RUNX2*, also involved in the development of hippocampal GABAergic neurons (Pleasure et al., 2000), and the generation of an extra source of GABAergic neurons resulting from the expansion of dorsal thalamic structures (Striedter 2004, Rakic 2009, Geschwind and Rakic 2013). Importantly, as reasoned in Murphy and Benítez-Burraco (2016b), hippocampal θ waves, which are produced by slow pulses of GABAergic inhibition (Vertes and Kocsis 1997), are involved in the extraction of language feature-sets from memory. Additionally, we expect that the language-specificity of our network rely as well on the role played by our candidates in FOXO and RAP1 pathways, contrary to the genes related to broader cognitive conditions like SZ and ASD. Regarding the FOXO signalling pathway, we have already discussed the relevance of *FOXP1* and *FOXP2*. We wish also highlight *FOXO1*, which is a target of the two core candidates for the evolutionary changes that prompted the emergence of our language-readiness, namely, *RUNX2* (Kuhlwilm et al. 2013) and *FOXP2* (Vernes et al. 2011) (see Boeckx and Benítez-Burraco 2014a, 2014b, and Benítez-Burraco and Boeckx 2015 for details). Additionally, FOXO1 upregulates *RELN* (Daly et al. 2004), a candidate for ASD and for lissencephaly with language loss (Hong et al. 2000, Wang et al. 2014), and is phosphorylated by DYRK1A (Huang and Tindall, 2007). Regarding the RAP1 signalling pathway, it is important for regulating MAPK activity and for promoting GABA(B) receptor surface

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expression (Zhang et al. 2015). As shown in Table 3, candidates for clinical conditions affecting language only are enriched in components of this pathway.

In order to delve into the language-specificity of our network, we also used Enrichr to generate the expression grids of our candidates for the oscillogenome across the brain regions profiled by the Allen Brain Atlas (http://www.brain-map.org/). Figure 2 compares the grids for up- and downregulated genes in the brain, with the grids for SZ, ASD, DD, and SLI. Overall, our candidates are most upregulated in the medial septal nucleus, which innervates the hippocampal formation and which plays a key role in the generation of θ waves (Pignatelli et al. 2012). They are also highly upregulated in the thalamus (specifically, in the sensory-motor cortex, but also in the stria terminalis, which serves as a major output pathway of the amygdala), the insula (in the ventral and the dorsal parts of the agranular insular area and in the superficial stratum of insular cortex), and in the striatum (in the septopallidal area, the striatal septum and the pallidal septum). They are significantly downregulated in several parts of the cerebellum, including the cerebellar cortex and the vermis. On the contrary, candidates for SLI are mostly upregulated in the basal forebrain and the hindbrain, whereas they are most downregulated in different areas of the cortex, including the retrosplenial, frontal, and parietal cortices. We think that this might contribute to confer an oscillomic specificity to our language-related set of candidates compared to other candidates for language dysfunction. As we discuss in detail in Boeckx and Benítez-Burraco (2014a), the thalamus may have played a central role in the evolutionary changes resulting in our language-readiness. The thalamus acts as a relay device for most of the brain areas involved in language processing, particularly, between the cortex and the basal ganglia (Lieberman 2002, Theyel et al. 2009), and it is crucially involved in aspects of the syntax-semantics interface (Wahl et al. 2008; David et al. 2011). Importantly for our hypothesis, the thalamus controls the oscillations generated in the cortex (Theyel et al. 2009, Saalmann et al., 2012). Specifically, thalamic input allows for an enrichment of oscillatory activity in different frequency bands (Singer 2013, Uhlhaas et al. 2013, Cannon et al. 2014), and it is thalamic GABAergic neurons that crucially contribute to restrict cortical activity, by providing low-frequency oscillations that are capable of embedding higher-frequency oscillations across distant brain areas (Whitman et al. 2013). This embedding plays a key role in aspects of language processing (see Boeckx 2013a,b and Murphy 2015b, 2016b for details). Regarding the striatum, it is crucially involved in vocal learning, as part of the cortico-thalamic-striatal circuits responsible for motor planning and procedural learning (for details, see Boeckx and Benítez-Burraco 2014b).

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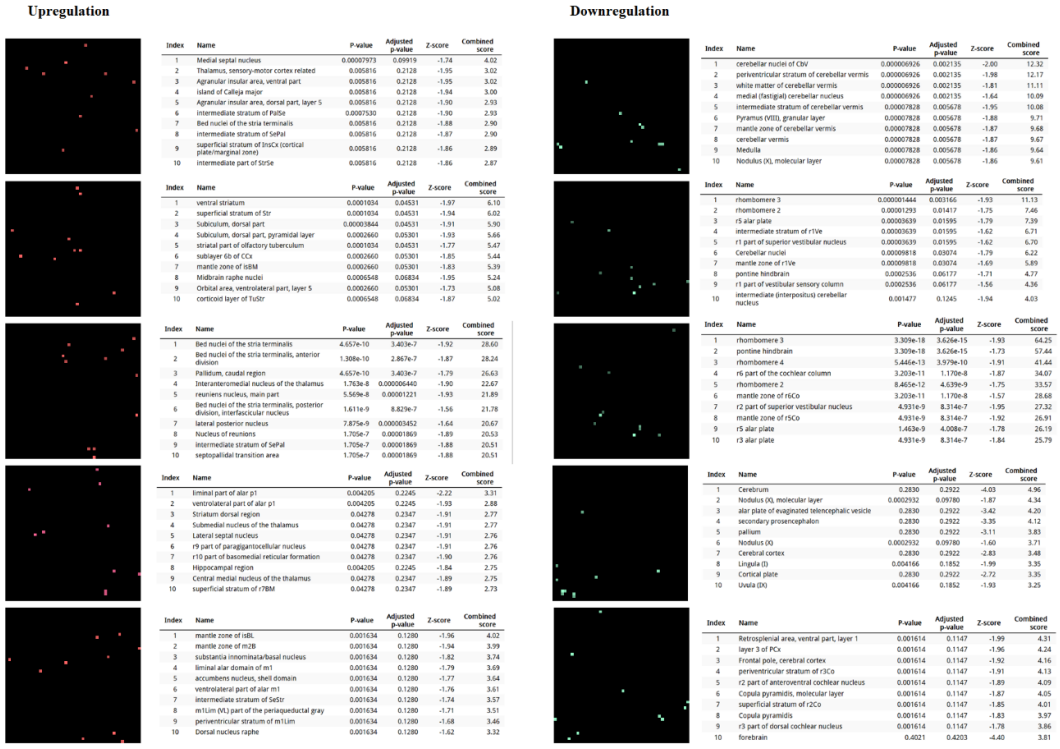

Upregulation

LO

Index	Name	P-value	Adjusted p-value	Z-score	Combined score
1	Medial septal nucleus	0.00007973	0.09919	-1.74	4.02
2	Thalamus, sensory-motor cortex related	0.005816	0.2128	-1.95	3.02
3	Agranular insular area, ventral part	0.005816	0.2128	-1.95	3.02
4	Island of Calleja major	0.005816	0.2128	-1.94	3.00
5	Agranular insular area, dorsal part, layer 5	0.005816	0.2128	-1.90	2.93
6	Intermediate stratum of PaSte	0.0007530	0.2128	-1.90	2.93
7	Bed nuclei of the stria terminalis	0.005816	0.2128	-1.88	2.90
8	Intermediate stratum of SePal	0.005816	0.2128	-1.87	2.90
9	superficial stratum of InsCx (cortical plate/marginal zone)	0.005816	0.2128	-1.86	2.89
10	Intermediate part of StrSe	0.005816	0.2128	-1.86	2.87

SZ

Index	Name	P-value	Adjusted p-value	Z-score	Combined score
1	ventral striatum	0.0001034	0.04531	-1.97	6.10
2	superficial stratum of Str	0.0001034	0.04531	-1.94	6.02
3	Subiculum, dorsal part	0.00003844	0.04531	-1.91	5.90
4	Subiculum, dorsal part, pyramidal layer	0.0002660	0.05301	-1.93	5.66
5	striatal part of olfactory tuberculum	0.0001034	0.04531	-1.77	5.47
6	sublayer 6b of CCx	0.0002660	0.05301	-1.85	5.44
7	mantle zone of isBM	0.0002660	0.05301	-1.83	5.39
8	Midbrain raphe nuclei	0.0006548	0.06834	-1.95	5.24
9	Orbital area, ventrolateral part, layer 5	0.0002660	0.05301	-1.73	5.08
10	corticoid layer of TuStr	0.0006548	0.06834	-1.87	5.02

ASD

Index	Name	P-value	Adjusted p-value	Z-score	Combined score
1	Bed nuclei of the stria terminalis	4.657e-10	3.403e-7	-1.92	28.60
2	Bed nuclei of the stria terminalis, anterior division	1.308e-10	2.867e-7	-1.87	28.24
3	Pallidum, caudal region	4.657e-10	3.403e-7	-1.79	26.63
4	Interanteromedial nucleus of the thalamus	1.763e-8	0.000006440	-1.90	22.67
5	reuniens nucleus, main part	5.569e-8	0.00001221	-1.93	21.89
6	Bed nuclei of the stria terminalis, posterior division, interfascicular nucleus	1.611e-9	8.829e-7	-1.56	21.78
7	lateral posterior nucleus	7.875e-9	0.000003452	-1.64	20.67
8	Nucleus of reunions	1.705e-7	0.00001869	-1.89	20.53
9	Intermediate stratum of SePal	1.705e-7	0.00001869	-1.88	20.51
10	septopallidal transition area	1.705e-7	0.00001869	-1.88	20.51

DD

Index	Name	P-value	Adjusted p-value	Z-score	Combined score
1	liminal part of alar p1	0.004205	0.2245	-2.22	3.31
2	ventrolateral part of alar p1	0.004205	0.2245	-1.93	2.88
3	Striatum dorsal region	0.04278	0.2347	-1.91	2.77
4	Submedial nucleus of the thalamus	0.04278	0.2347	-1.91	2.77
5	Lateral septal nucleus	0.04278	0.2347	-1.91	2.76
6	r9 part of paragigantocellular nucleus	0.04278	0.2347	-1.91	2.76
7	r10 part of basomedial reticular formation	0.04278	0.2347	-1.90	2.76
8	Hippocampal region	0.004205	0.2245	-1.84	2.75
9	Central medial nucleus of the thalamus	0.04278	0.2347	-1.89	2.75
10	superficial stratum of r7BM	0.04278	0.2347	-1.89	2.73

SLI

Index	Name	P-value	Adjusted p-value	Z-score	Combined score
1	mantle zone of isBL	0.001634	0.1280	-1.96	4.02
2	mantle zone of m2B	0.001634	0.1280	-1.94	3.99
3	substantia innominata/basal nucleus	0.001634	0.1280	-1.82	3.74
4	liminal alar domain of m1	0.001634	0.1280	-1.79	3.69
5	accumbens nucleus, shell domain	0.001634	0.1280	-1.77	3.64
6	ventrolateral part of alar m1	0.001634	0.1280	-1.76	3.61
7	intermediate stratum of SeStr	0.001634	0.1280	-1.74	3.57
8	m1Lim (VL) part of the periaqueductal gray	0.001634	0.1280	-1.71	3.51
9	periventricular stratum of m1Lim	0.001634	0.1280	-1.68	3.46
10	Dorsal nucleus raphe	0.001634	0.1280	-1.62	3.32

Downregulation

LO

Index	Name	P-value	Adjusted p-value	Z-score	Combined score
1	cerebellar nuclei of CbV	0.000006926	0.002135	-2.00	12.32
2	periventricular stratum of cerebellar vermis	0.000006926	0.002135	-1.98	12.17
3	white matter of cerebellar vermis	0.000006926	0.002135	-1.81	11.11
4	medial (fastigial) cerebellar nucleus	0.000006926	0.002135	-1.64	10.09
5	intermediate stratum of cerebellar vermis	0.00007828	0.005678	-1.95	10.08
6	Pyramus (VIII), granular layer	0.00007828	0.005678	-1.88	9.71
7	mantle zone of cerebellar vermis	0.00007828	0.005678	-1.87	9.68
8	cerebellar vermis	0.00007828	0.005678	-1.87	9.67
9	Medulla	0.00007828	0.005678	-1.86	9.64
10	Nodulus (X), molecular layer	0.00007828	0.005678	-1.86	9.61

SZ

Index	Name	P-value	Adjusted p-value	Z-score	Combined score
1	rhombomere 3	0.000001444	0.003166	-1.93	11.13
2	rhombomere 2	0.00001293	0.01417	-1.75	7.46
3	r5 alar plate	0.00003639	0.01595	-1.79	7.39
4	intermediate stratum of r1Ve	0.00003639	0.01595	-1.62	6.71
5	r1 part of superior vestibular nucleus	0.00003639	0.01595	-1.62	6.70
6	Cerebellar nuclei	0.00009818	0.03074	-1.79	6.22
7	mantle zone of r1Ve	0.00009818	0.03074	-1.69	5.89
8	pontine hindbrain	0.0002536	0.06177	-1.71	4.77
9	r1 part of vestibular sensory column	0.0002536	0.06177	-1.56	4.36
10	intermediate (interpositus) cerebellar nucleus	0.001477	0.1245	-1.94	4.03

ASD

Index	Name	P-value	Adjusted p-value	Z-score	Combined score
1	rhombomere 3	3.309e-18	3.626e-15	-1.93	64.25
2	pontine hindbrain	3.309e-18	3.626e-15	-1.73	57.44
3	rhombomere 4	5.446e-13	3.979e-10	-1.91	41.44
4	r6 part of the cochlear column	3.203e-11	1.170e-8	-1.87	34.07
5	rhombomere 2	8.465e-12	4.639e-9	-1.75	33.57
6	mantle zone of r6Co	3.203e-11	1.170e-8	-1.57	28.68
7	r2 part of superior vestibular nucleus	4.931e-9	8.314e-7	-1.95	27.32
8	mantle zone of r5Co	4.931e-9	8.314e-7	-1.92	26.91
9	r5 alar plate	1.463e-9	4.008e-7	-1.78	26.19
10	r3 alar plate	4.931e-9	8.314e-7	-1.84	25.79

DD

Index	Name	P-value	Adjusted p-value	Z-score	Combined score
1	Cerebrum	0.2830	0.2922	-4.03	4.96
2	Nodulus (X), molecular layer	0.0002932	0.09780	-1.87	4.34
3	alar plate of evaginated telencephalic vesicle	0.2830	0.2922	-3.42	4.20
4	secondary prosencephalon	0.2830	0.2922	-3.35	4.12
5	pallium	0.2830	0.2922	-3.11	3.83
6	Nodulus (X)	0.0002932	0.09780	-1.60	3.71
7	Cerebral cortex	0.2830	0.2922	-2.83	3.48
8	Lingula (I)	0.004166	0.1852	-1.99	3.35
9	Cortical plate	0.2830	0.2922	-2.72	3.35
10	Uvula (IX)	0.004166	0.1852	-1.93	3.25

SLI

Index	Name	P-value	Adjusted p-value	Z-score	Combined score
1	Retrosplenial area, ventral part, layer 1	0.001614	0.1147	-1.99	4.31
2	layer 3 of PCx	0.001614	0.1147	-1.96	4.24
3	Frontal pole, cerebral cortex	0.001614	0.1147	-1.92	4.16
4	periventricular stratum of r3Co	0.001614	0.1147	-1.91	4.13
5	r2 part of anteroventral cochlear nucleus	0.001614	0.1147	-1.89	4.09
6	Copula pyramidis, molecular layer	0.001614	0.1147	-1.87	4.05
7	superficial stratum of r2Co	0.001614	0.1147	-1.85	4.01
8	Copula pyramidis	0.001614	0.1147	-1.83	3.97
9	r3 part of dorsal cochlear nucleus	0.001614	0.1147	-1.78	3.86
10	forebrain	0.4021	0.4203	-4.40	3.81

Figure 2. Expression profiles in the brain of the set of genes considered in this study. Expression grids were generated with Enrichr. Brain regions where genes are most upregulated are displayed in red, whereas region in which genes are most downregulated are shown in green (the more light the colour, the more up- or downregulated a gene is). The tables contain the most up- or downregulated genes according to the Combined Score. The acronyms for the brain regions are from the Allen Brain Atlas and can be checked at http://developingmouse.brain-map.org/docs/Legend_2010_03.pdf.

We have equally examined the brain expression profiles of our candidates across development, in order to know whether they are down- or upregulated during the time window when changes in the brain wiring and function, important for language acquisition, take place. As shown in figure 3, some of these genes exhibit expression peaks in different brain areas between 0-5 years of age, like *APOE*, *CX3CR1*, *CYP19A1*, and *PDGFRB*. Conversely, others are significantly downregulated after birth, like *COL4A2*, *DLX5*, *GRIN2B*, *ROBO1*, or *SETBP1*. Interestingly, several of our candidates exhibit dissimilar expression trends in different brain areas. For instance, after birth, *CACNA1L* is upregulated in the striatum and downregulated in the thalamus. Likewise, *CX3CR1* is downregulated in the cerebellum and upregulated in the cortex, the thalamus, and the striatum. Because of the involvement of the thalamus in our model of language processing and language evolution, it is also of interest the expression profile of *CYP19A1* in this area, with a neat peak during childhood. Also of interest is *HTR1A*, with shows consecutive expression peaks across development: it is highly expressed in the embryonic cortex and the embryonic hippocampus (with a second peak during adolescence), it is upregulated in the cerebellum around birth, and it is upregulated in the amygdala in young people. We expect that these patterns of expression contribute to explain the observed changes in brain activity during language processing across developmental stages, and ultimately, account for some of the changes in the language abilities of the child.

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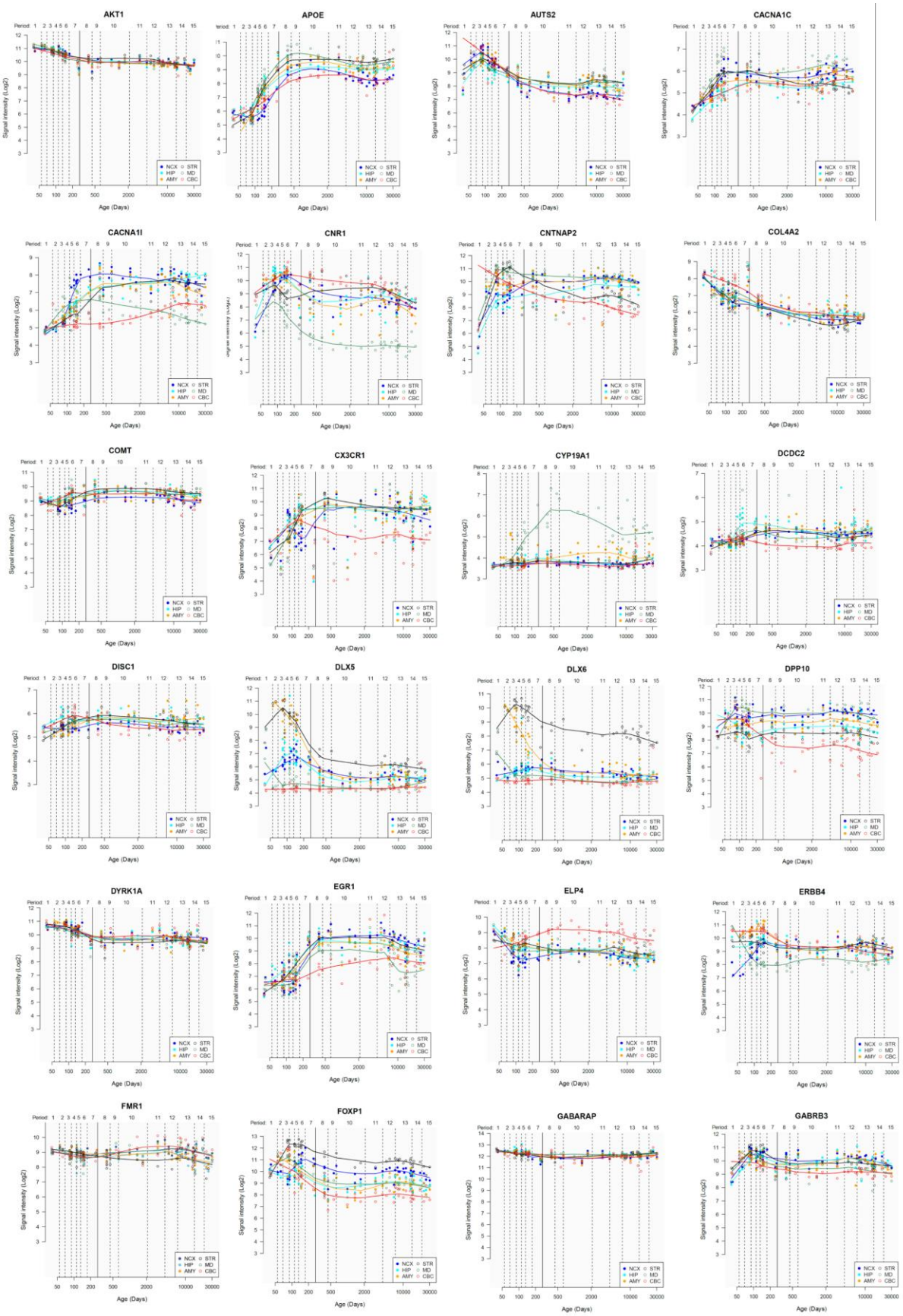

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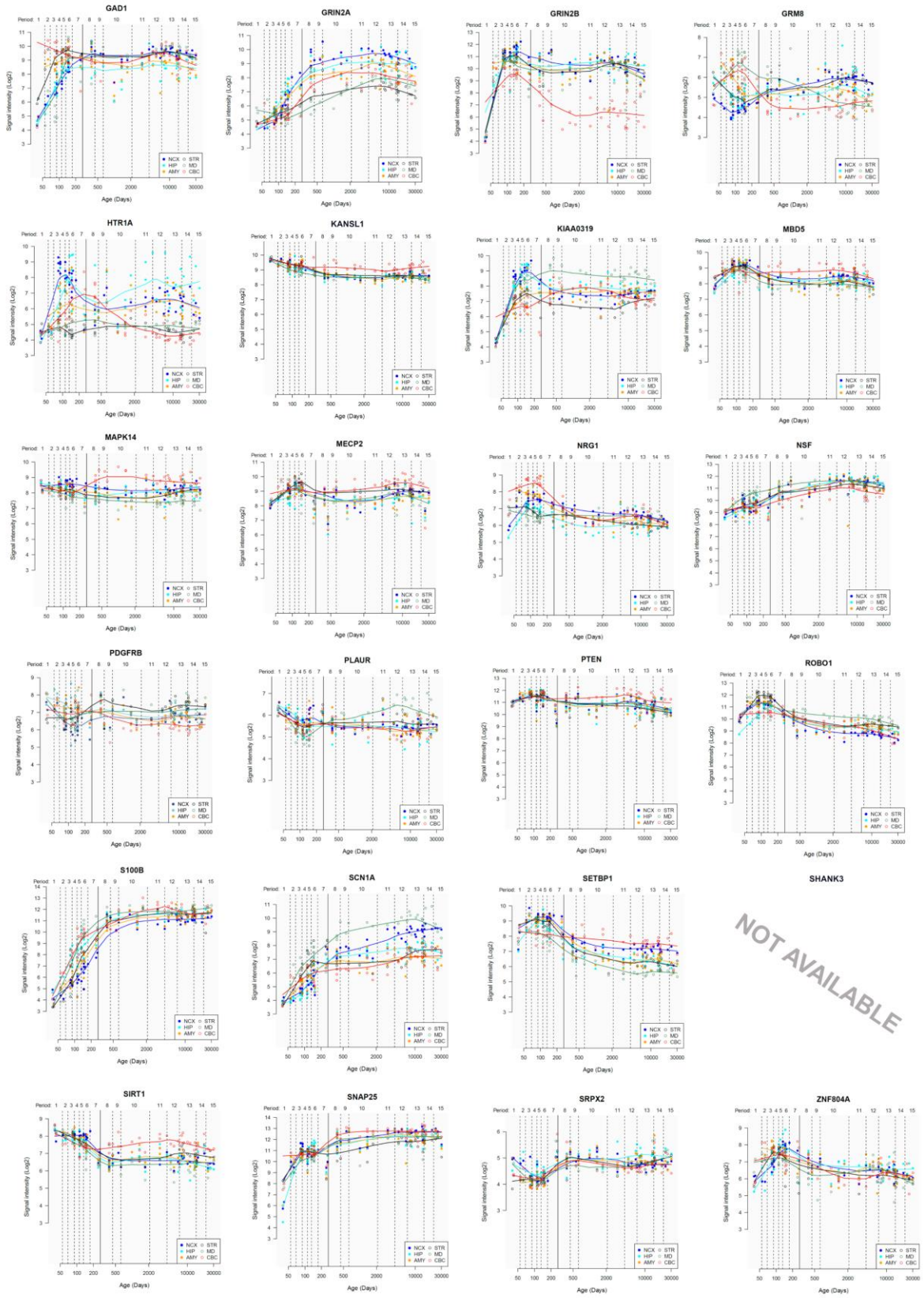

Figure 3. Individual brain expression profiles across development of the set of genes considered in this study. The expression data are from the Human Brain Transcriptome Database (http://hbatlas.org/). Six different brain regions are considered: the cerebellar cortex (CBC), the mediodorsal nucleus of the thalamus (MD), the striatum (STR), the amygdala

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(AMY), the hippocampus (HIP) and 11 areas of neocortex (NCX). Data for *SHANK3* were not available.

3. Linking the language oscillogenome to language processing

Having documented the most likely candidates which could constitute a robust, testable 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.

In Murphy (2016b), an 'oscillomic' model was proposed through which linguistic representations are itemized via γ nesting within parahippocampal θ cycles. 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. Ewerdwalbesloh et al. (2016) show that holding visually constructed objects in memory (as opposed to 'whole', presented object) results in greater fronto-parietal θ synchronisation. Since the maintenance of constructed objects in fronto-parietal circuits is vital for language, it was hypothesized in Murphy (2016b) that the language system might recruit this (possibly generic) neural code for computationally analogous purposes. In brief, a lexicalisation process generated by a θ-γ code would interact with a phrasal construction process of δ phase-entrainment. 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.

What are the reasons to believe that oscillations have any causal-explanatory power with respect to language? Vosskuhl et al. (2015) used transcranial alternating current stimulation (tACS) to decrease participant's θ such that the θ:γ ratio was altered and a larger number of γ cycles could be nested within θ. This carefully controlled study demonstrated that this manipulation increased working memory performance. Although this study does not directly speak to syntactic combinatorics, given the reliance the language system has on working memory we can infer that the θ-γ code is causally related to linguistic representation construction.

Other experimental evidence for the role of this neural code in language comes from a number of places, such as the finding that left-cortical δ entrains to hierarchical linguistic structures

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from syllables to sentences (Ding et al. 2016). In addition, the roles ascribed here to particular oscillations and oscillatory interactions are supported by the broader (often domain-general) roles argued for by Ketz et al. (2015); namely, that θ is implicated in recollective memory, β in executive control, and α in sensory information gating. In addition, α decreases at right fronto-temporal sites occur when syllables are temporally expected (Wilsch et al. 2015). Such expectancy effects appear in other linguistic domains, with increased semantic predictability leading to reduced parieto-occipital α (Wöstmann et al. 2015). Finally, a verbal generation task by Wojtecki et al. (2016) resulted in 6-12Hz power increases and enhanced θ-α coherence between the subthalamic nucleus and frontal sites as a function of successful task performance. Despite the relative paucity of experimental work, the role of α in semantic and phonological prediction seems clear – in particular given this rhythm's function in coordinating the representations constructed by θ-γ coupling (as reviewed in 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). Increased γ power has also been found for individuals with autism (Kikuchi et al. 2013; Rojas et al. 2008), likely going some way to explain their abnormal linguistic comprehension given the model discussed in Murphy (2016b), with Kikuchi et al. finding in addition reduced cross-cortical θ, α and β. Bangel et al. (2014) discovered lower β power during a number estimation task in individuals with ASD, and broader rhythmic abnormalities have been found. 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 play 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 effects 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.

Abnormally long-lasting prefrontal and central γ is exhibited by individuals with ASD during processing semantic incongruities (Braeutigam et al. 2008), which potentially reflects the execution of a general search mechanism (high γ) to replace the normal rhythmic processes (low γ) to extract and compare 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 lead to lower left inferior frontal γ and β power in ASD

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subjects relative to neurotypical controls (Buard et al. 2013), and rhythmic connectivity between auditory and language cortices is also abnormal (Jochaut et al. 2015); results potentially explicable via this oscillogenomic account. In particular, Jochaut et al. discovered that speech processing results in severely impaired θ-γ coupling 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.

A study of lexical decision in SZ also exposed lower left-temporal and left-frontal α and β power (Xu et al.'s 2013) – a rhythmic profile also found in Moran and Hong (2011) and Uhlhaas et al. (2008). A sentence presentation task by Xu et al. (2012) revealed reduced θ at 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 linguistic prosody, 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 anticipatory δ phase-synchronization. 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 strongly reflective of dysphonetic dyslexics (with grapheme-to-phoneme conversion difficulties) whereas increased posterior β are typically found in dyseidetic children (with problems accessing the visual lexicon) (Flynn

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et al. 1992). These findings are compatible with the model proposed in Murphy (2016b) and discussed above, 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 neurotypicals, dyslexics additionally display 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.

Because many of the the computational roles we have ascribed to oscillations are notably generic (with the exception of language-specific δ-driven phrasal construction), this genericity of neurocognitive function can potentially map on to the Generalist Genes Hypothesis (Plomin & Kovas 2005; Kovas & Plomin 2006), such that the genes we have here claimed to be relevant to specific linguistic deficits (be it syntactic, phonological, and so on) are also likely implicated in other cognitive capacities, by virtue of the generic computational roles of, for instance, the θ-γ code or α inhibition.

There are alternative accounts to the one presented here which downplay (or simply reject) the existence of any causal-explanatory role for oscillations in language. For instance, Goucha et al. (2017) claim that 'those [oscillatory] mechanisms seem to already be in place in other species. For example, despite the crucial brain expansion that took place in primates and especially humans compared to other mammals, the rhythmical hierarchy of oscillations is mainly kept unchanged'. While it may be true that this hierarchy has 'mainly' been kept unchanged – as indeed recent neuroethological work by Kikuchi et al. (2017) attempts to show – thus far there have been no neuroethological experiments using the kind of stimuli which would allow researchers to compare the oscillatory basis of putatively human-specific

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computations (like phrase-structure building) to the neural responses of non-human primates attempting to interpret or parse identical structures. Kikuchi et al. simply expose humans and monkeys to artificial grammars; not only does this not guarantee that the human subjects would recruit their language systems, but even if it did Kikuchi et al.'s data analysis did not investigate the kind of cross-frequency couplings over the particular regions and rhythms claimed here to be responsible for phrase-structure building. For instance, Kikuchi et al. only examine coupling between low frequencies and γ (see their Figure 4), and not coupling between low frequencies such as δ, θ and β (or indeed phase-phase coupling, claimed in Murphy 2016b to potentially play a role in syntactic processing). The authors found that 'learned ordering relationships modulate the observed form of neural oscillatory coupling in [humans and monkeys]', but this is a far cry from interpreting or generating hierarchically structured expressions. Indeed, further testing the model outlined here could involve not only refining Kikuchi et al.'s study to involve a broader class of stimuli and analyses, but it could also involve using MEG and EEG to investigate the oscillatory responses in people with autism and schizophrenia during language comprehension, going some way to lend more direct, experimental forms of support.

As a way of modelling what we have discussed here, Figure 4 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.

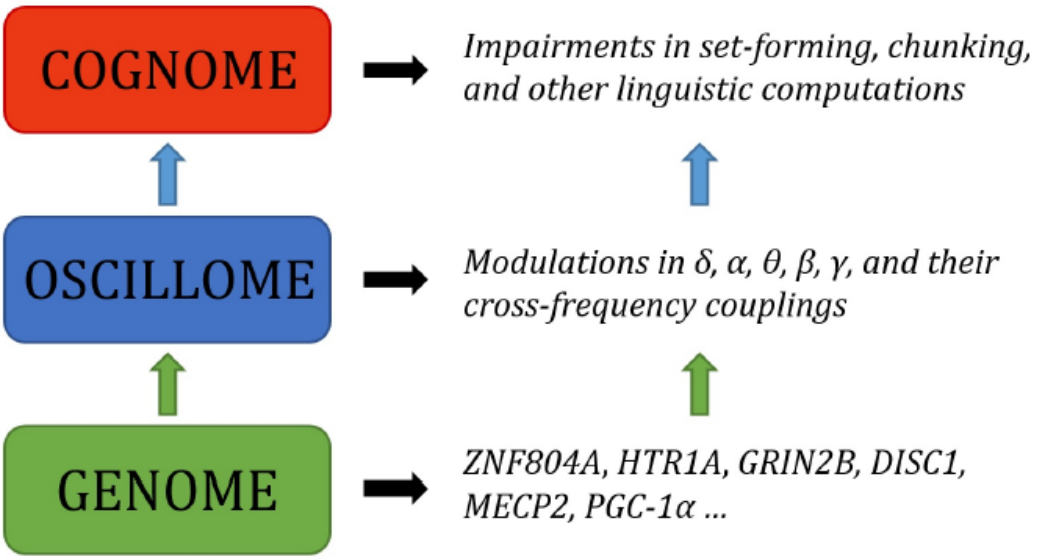

Figure 4. Outline of a putative oscillogenomic model for the human faculty of language. ASD, SZ, SLI and DD have been used as guiding 'oscillopathies', whereas linguistic theory has been employed as a guide for the neurocomputational basis of language. The genome is expected to modulate frequency bands 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). For instance, as noted in the text, knockout of *Ppargc1a* in mice decreases the spread of activation in hippocampal CA1 and limits pyramidal cell spiking, leading to unusual modulations of kainate-induced γ.

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PPARGC1A deficiency in ASD may consequently lead to direct oscillatory alterations at this frequency band; a hypothesis pending experimental confirmation.

4. Conclusions

Contemporary sequencing technologies have greatly expanded the set of genes associated with cognitive conditions entailing language deficits. The polygenism seen in these diseases is somewhat commensurable with the polygenism expected for language, which is necessary to properly characterize if we want to understand how language unfolds in the brain and develops 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 through 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 (Figure 5). 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. There are also a number of potentially fruitful avenues to follow with respect to testing some of the core claims made here. For instance, if a given population (e.g. individuals with dyslexia) are known to exhibit particular genetic disruptions which are relevant to the generation of certain brain rhythms (e.g. δ), then this population could undergo M/EEG testing to determine if the linguistic capacities discussed here (e.g. phonological processing) are indeed disrupted in the manner predicted.

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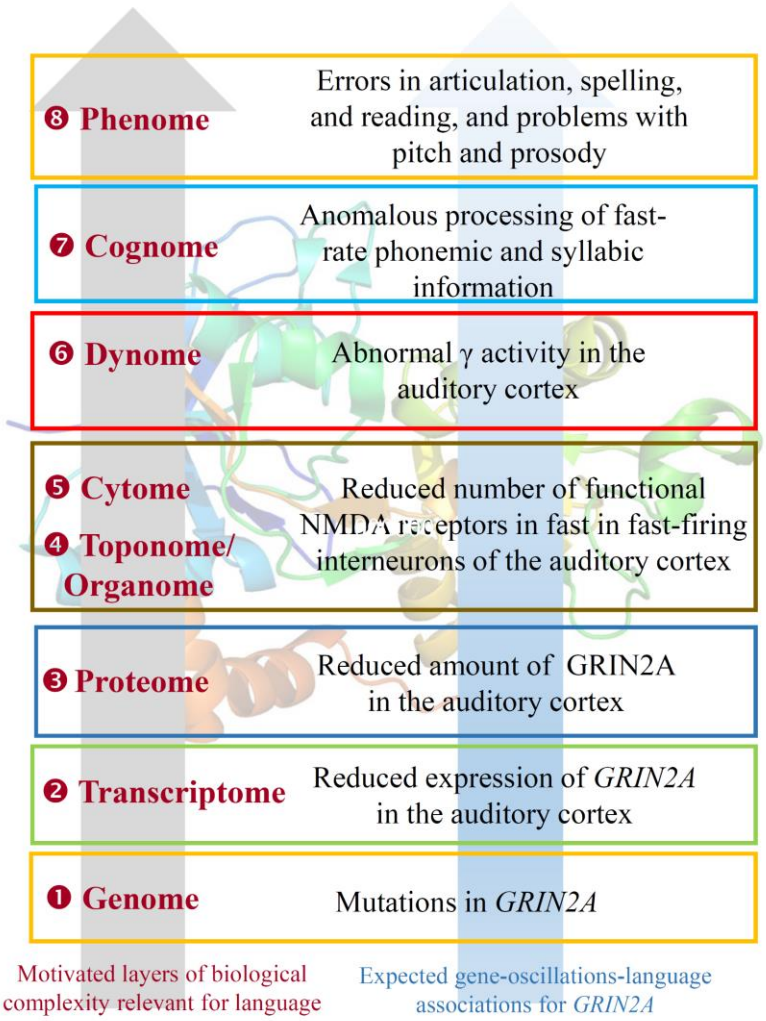

Figure 5. ***GRIN2A* as an example of the observed (and expected) bridging links across the different levels of the biological analysis of language**. As highlighted in the text, mutations in the gene give rise to different forms of epilepsy-aphasias, like Landau-Kleffner syndrome, continuous spike and waves during slow-wave sleep syndrome, and rolandic epilepsies. *GRIN2A* expression is found in several brain areas; a noteworthy upregulation of the gene is observed during late embryonic development. *GRIN2A* encodes the subunit 2A of the NMDA receptor, which plays a key role in long-term potentiation, a physiological process important for memory and learning. This role seemingly results in part from its effect on γ oscillation formation and modulation. As also noted in the text, GRIN2A levels are reduced in fast-firing interneurons of people with schizophrenia. As also discussed, mutations in *GRIN2A* result in errors in articulation, and in problems with pitch and prosody, which pertain to linguistic prosody, and which can be tracked to the abnormal γ activity, which is crucial for the correct processing of fast-rate phonemic and syllabic information. The 3D structure of GRIN2A, inserted as the background of the picture, is from the RSCB Protein Data Bank (http://www.rcsb.org/pdb/home/home.do). Here, 'genome' refers to the set of genes related to brain rhythms that are relevant for language, 'transcriptome', to their RNA products, and 'proteome' to the proteins they encode. 'Toponome' refers to the whole set of codes of proteins and other biomolecules found in the cells surface, whereas 'Organome' refers to the set of cell signalling molecules involved in cell and organ crosstalk. 'Cytome' refers to the collection of different cell types of the organism. 'Connectome' refers to the wiring of brain areas involved

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in language processing. 'Dynome' refers to the brain dynamics underlying (and supporting) this processing, in the line of Kopell et al., 2014 and Murphy, 2015. 'Cognome' refers to the basic cognitive operations underlying language (and in this case, speech processing), in the line of Poeppel, 2012. Finally, 'phenome' refers to the discrete, language-specific activities (in this case, phonological and phonetic aspects of speech).

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 gain 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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References

Addis, L., Ahn, J. W., Dobson, R., Dixit, A., Ogilvie, C. M., Pinto, D., et al., 2015. Microdeletions of ELP4 are associated with language impairment, autism spectrum disorder, and mental retardation. Hum. Mutat. 36, 842-50.

Amiri, A., Cho, W., Zhou, J., Birnbaum, S. G., Sinton, C. M., McKay, R. M., et al., 2012. Pten deletion in adult hippocampal neural stem/progenitor cells causes cellular abnormalities and alters neurogenesis. J Neurosci. 32, 5880-90. doi: 10.1523/JNEUROSCI.5462-11.2012.

Anderson, M.L. 2016. Précis of After Phrenology: Neural Reuse and the Interactive Brain. Behavioral and Brain Sciences doi:10.1017/S0140525X15000631, e120.

Anitha, A., Nakamura, K., Thanseem, I., Yamada, K., Iwayama, Y., Toyota, T., et al., 2012. Brain region-specific altered expression and association of mitochondria-related genes in autism. Mol Autism. 3, 12. doi: 10.1186/2040-2392-3-12.

Arcuri C., Bianchi R, Brozzi F, Donato R., 2005. S100B increases proliferation in PC12 neuronal cells and reduces their responsiveness to nerve growth factor via Akt activation. J Biol Chem 280, 4402-14.

Bae, M. H., Bissonette, G. B., Mars, W. M., Michalopoulos, G. K., Achim, C. L., Depireux, D. A., et al.,2010. Hepatocyte growth factor (HGF) modulates GABAergic inhibition and seizure susceptibility. Exp Neurol. 221, 129-35. doi: 10.1016/j.expneurol.2009.10.011.

Balu DT, Carlson GC, Talbot K, Kazi H, Hill-Smith TE, Easton RM, Birnbaum MJ, Lucki I., 2012. Akt1 deficiency in schizophrenia and impairment of hippocampal plasticity and function. Hippocampus 22, 230-40.

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Bangel, K.A., Batty, M., Ye., A. X., Meaux, E., Taylor, M.J., Doesburg S.M., 2014. Reduced beta band connectivity during number estimation in autism. NeuroImageClinl6, 202-213.

Bartley, A.F., Lucas, E.K., Brady, L.J., Li, Q., Hablitz, J.J., Cowell, R.M., et al., 2015. Interneuron transcriptional dysregulation causes frequency-dependent alterations in the balance of inhibition and excitation in hippocampus. J Neurosci 35, 15276-90.

Battaglia D, Chieffo D, Siracusano R, Waure Cd, Brogna C, Ranalli D, Contaldo I, Tortorella G, Dravet C, Mercuri E, Guzzetta F, 2013. Cognitive decline in Dravet syndrome: is there a cerebellar role? Epilepsy Res 106, 211-21

Becker, J., Czamara, D., Hoffmann, P., Landerl, K., Blomert, L., Brandeis, D., et al. 2012. Evidence for the involvement of ZNF804A in cognitive processes of relevance to reading and spelling. Transl. Psychiatry 2, e136.

Begleiter, H., Porjesz, B., 2006. Genetics of human brain oscillations. Int J Psychophysiol 60, 162-171.

Benítez-Burraco, A., Murphy, E., 2016. The oscillopathic nature of language deficits in autism: from genes to language evolution. Front. Hum. Neurosci. 10, 120.

Berman, J.I., Liu, S., Bloy, L., Blaskey, L., Roberts, T.P.L., Edgar, J.C., 2015. Alpha-to-gamma phase-amplitude coupling methods and application to autism spectrum disorder. Brain Connect 5, 80-90.

Berwick, R.C., Chomsky, N. 2015. Foreword: A bird's-eye view of human language and evolution, in: Bolhuis, J.J., Everaert, M. (Eds.), Birdsong, Speech, and Language: Exploring the Evolution of Mind and Brain. Cambridge, MA, MIT Press. pp. ix-xii.

Bishop, D.V.M., Hardimann, M.J.,Barry, J.G., 2010. Lower-frequency event-related desynchronization: a signature of late mismatch responses to sounds, which is reduced or absent in children with specific language impairment. J Neurosci 30, 15578-15584.

Boeckx C, 2013a. Biolinguistics: Forays into human cognitive biology. J Anthropol Sci 91,63-89

Boeckx C, 2013b. On Merge: Biolinguistic considerations. Engl Linguist 30, 463–484

Bond, A. M., Vangompel, M. J., Sametsky, E. A., Clark, M. F., Savage, J. C., Disterhoft, J.F., et al., 2009. Balanced gene regulation by an embryonic brain ncRNA is critical for adult hippocampal GABA circuitry. Nat Neurosci. 12, 1020-7. doi: 10.1038/nn.2371.

Booth, C. A., Brown, J. T., Randall, A. D., 2014. Neurophysiological modification of CA1 pyramidal neurons in a transgenic mouse expressing a truncated form of disrupted-in-schizophrenia 1. Eur. J. Neurosci. 39, 1074-90.

Bouaboula, M., Bourrié, B., Rinaldi-Carmona, M., Shire, D., Le Fur, G., Casellas P. 1995. Stimulation of cannabinoid receptor CB1 induces krox-24 expression in human astrocytoma cells. J Biol Chem. 270, 13973-80.

Braeutigam, S., Swithenby, S.J., Bailey, A.J., 2008. Contextual integration the unusual way: a magnetoencephalographic study of responses to semantic violation in individuals with autism spectrum disorder. Eur. J. Neurosci. 27, 1026-1036.

Braida, D., Guerini, F. R., Ponzoni, L., Corradini, I., De Astis, S., Pattini, L., et al., 2015. Association between SNAP-25 gene polymorphisms and cognition in autism: functional consequences and potential therapeutic strategies. Transl Psychiatry 5, e500. doi: 10.1038/tp.2014.136.

Brandon, N.J.,Sawa, A., 2011. Linking neurodevelopmental and synaptic theories of mental illness through DISC1. Nat. Rev. Neurosci. 12, 707-22.

Brohée S, van Helden J., 2006. Evaluation of clustering algorithms for protein-protein interaction networks BMC Bioinformatics 7, 488.

Bruneau, N., Szepetowski, P., 2011. The role of the urokinase receptor in epilepsy, in disorders of language, cognition, communication and behavior, and in the central nervous system. Curr Pharm Des17, 1914-23.

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Buard, I., Rogers, S.J., Hepbum, S., Kronberg, E., Rojas, D.C., 2013. Altered oscillation patterns and connectivity during picture naming in autism. Front. Hum. Neurosci. 7, 742.

Buxbaum, J. D., Cai, G., Chaste, P., Nygren, G., Goldsmith, J., Reichert, J., et al. 2007. Mutation screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly. Am. J. Med. Genet. B Neuropsychiatr. Genet. 144B, 484-91.

Callaway, E., 1983. The pharmacology of human information processing. Psychopharmacologia 20, 359-370.

Cannon, J., McCarthy, M. M., Lee, S., Lee, J., Börgers, C., Whittington, M. A., Kopell, N, 2014. Neurosystems: brain rhythms and cognitive processing. Eur J Neurosci 39,705-19

Canuet L, Tellado I, Couceiro V, Fraile C, Fernandez-Novoa L, Ishii R, Takeda M, Cacabelos R, 2012. Resting-state network disruption and APOE genotype in Alzheimer's disease: a lagged functional connectivity study. PLoS One 7, e46289.

Carr, C. W., Moreno-De-Luca, D., Parker, C., Zimmerman, H. H., Ledbetter, N., Martin, C. L., et al., 2010. Chiari I malformation, delayed gross motor skills, severe speech delay, and epileptiform discharges in a child with FOXP1 haploinsufficiency. Eur J Hum Genet. 18, 1216-20. doi: 10.1038/ejhg.2010.96.

Chakrabarti, B., Kent, L., Suckling, J., Bullmore, E., Baron-Cohen, S., 2006. Variations in the human cannabinoid receptor (CNR1) gene modulate striatal responses to happy faces. Eur J Neurosci. 23, 1944-8.

Chang CY, Chen YW, Wang TW, Lai WS, 2016. Akting up in the GABA hypothesis of schizophrenia: Akt1 deficiency modulates GABAergic functions and hippocampus-dependent functions. Sci Rep 6, 33095.

Chao, H. T., Chen, H., Samaco, R. C., Xue, M., Chahrour, M., Yoo, J., et al., 2010. Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. Nature 468, 263-9.

Chen, A.C.H., Tang, Y., Rangaswamy, M., Wang, J.C., Almasy, L., Foroud, T., et al., 2009. Association of single nucleotide polymorphisms in a glutamate receptor gene (GRM8) with theta power of event-related oscillations and alcohol dependence. Am J Med Genet B Neuropsychiatr Genet. 150B, 359-368.

Chen, X. S., Reader, R. H., Hoischen, A., Veltman, J. A., Simpson, N. H., SLI Consortium, et al., 20176.Next-generation sequencing identifies novel gene variants and pathways involved in specific language impairment. Sci Rep. 7:, 46105.

Cho, K. K., Hoch, R., Lee, A. T., Patel, T., Rubenstein, J. L, Sohal, V. S., 2015. Gamma rhythms link prefrontal interneuron dysfunction with cognitive inflexibility in Dlx5/6(+/-) mice. Neuron 85, 1332-43.

Clipperton-Allen, A. E, Page, D. T.,2014. Pten haploinsufficient mice show broad brain overgrowth but selective impairments in autism-relevant behavioral tests. Hum Mol Genet. 23, 3490–3505. doi: 10.1093/hmg/ddu057.

Cobos, I., Long, J. E., Thwin, M. T., Rubenstein, J. L., 2006. Cellular patterns of transcription factor expression in developing cortical interneurons. Cereb. Cortex. 16, 82-88.

Coe, B.P., Witherspoon, K., Rosenfeld, J.A., van Bon, B.W., Vulto-van Silfhout, A.T., Bosco, P., et al., 2014. Refining analyses of copy number variation identifies specific genes associated with developmental delay. Nat Genet. 46,1063-71. doi: 10.1038/ng.3092.

Courcet, J. B., Faivre, L., Malzac, P., Masurel-Paulet, A., López, E., Callier, P., et al. 2012. The DYRK1A gene is a cause of syndromic intellectual disability with severe microcephaly and epilepsy. J. Med. Genet. 49, 731-6.

Cousijn, H., Tunbridge, E. M., Rolinski, M., Wallis, G., Colclough, G. L., Woolrich, M. W., et al. 2015. Modulation of hippocampal theta and hippocampal-prefrontal cortex function by a schizophrenia risk gene. Hum. Brain Mapp. 36, 2387-95.

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Creppe, C., Malinouskaya, L., Volvert, M. L., Gillard, M., Close, P., Malaise, O., et al. 2009. Elongator controls the migration and differentiation of cortical neurons through acetylation of alpha-tubulin. Cell 136, 551-64.

Cutini, S., Szűcs, D., Mead, N., Huss, M., Goswami, U. 2016. Atypical right hemisphere response to slow temporal modulations in children with developmental dyslexia. Neuroimage 143, 40-49. doi:10.1016/j.neuroimage.2016.08.012.

Daly C, Wong V, Burova E, Wei Y, Zabski S, Griffiths J, Lai KM, Lin HC, Ioffe E, Yancopoulos GD, Rudge JS, 2004. Angiopoietin-1 modulates endothelial cell function and gene expression via the transcription factor FKHR (FOXO1). Genes Dev 18, 1060-71.

Damaj, L., Lupien-Meilleur, A., Lortie, A., Riou,É.,Ospina, L. H., Gagnon, L., et al., 2015. CACNA1A haploinsufficiency causes cognitive impairment, autism and epileptic encephalopathy with mild cerebellar symptoms. Eur J Hum Genet. 23, 1505-12. doi: 10.1038/ejhg.2015.21.

Dasari, V. R., Kaur, K., Velpula, K. K., Gujrati, M., Fassett, D., Klopfenstein, J. D., et al. 2010. Upregulation of PTEN in glioma cells by cord blood mesenchymal stem cells inhibits migration via downregulation of the PI3K/Akt pathway. PLoS One 5, e10350.

David, O., Maess, B., Eckstein, K., Friederici, A. D, 2011. Dynamic causal modeling of subcortical connectivity of language. J. Neurosci. 31, 2712-2717.

de Miranda AS, Zhang CJ, Katsumoto A, Teixeira AL, 2017. Hippocampal adult neurogenesis: Does the immune system matter? J Neurol Sci 372, 482-495

Ding, N., Melloni, L., Zhang, H., Tian, X., & Poeppel, D. 2016. Cortical tracking of hierarchical linguistic structures in connected speech. Nature Neuroscience 19, 158-164.

Doesburg, S.M., Vidal, J., Taylor, M.J., 2013. Reduced theta connectivity during set-shifting in children with autism. Front. Hum. Neurosci. 7, 785.

Ehrlichman, R.S., Luminais, S.N., White, S.L., Rudnickm N.D., Mam N., Dowm H.C., et al., 2009. Neuregulin 1 transgenic mice display reduced mismatch negativity, contextual fear conditioning and social interactions. Brain Res 1294, 116-27. doi: 10.1016/j.brainres.2009.07.065.

Enoch, M.A., Xu, K., Ferro, E., Harris, C.R., Goldman, D., 2003. Genetic origins of anxiety in women: a role for a functional catechol-O-methyltransferase polymorphism. Psychiatr. Genet.13, 33–41.

Ewerdwalbesloh, J.A., Palva, S., Rösler, F.,Khader, P.H., 2016. Neural correlates of maintaining generated images in visual working memory. Hum Brain Mapp37, 4349-4362. doi:10.1002/hbm.23313.

Fatemi, S.H, Folsom, T.D, Kneeland, R.E, Liesch, S.B., 2011. Metabotropic glutamate receptor 5 upregulation in children with autism is associated with underexpression of both Fragile X mental retardation protein and GABAA receptor beta 3 in adults with autism. Anat Rec (Hoboken) 294, 1635-45. doi: 10.1002/ar.21299.

Filges I, Shimojima K, Okamoto N, Röthlisberger B, Weber P, Huber AR, Nishizawa T, Datta AN, Miny P, Yamamoto T, 2011. Reduced expression by SETBP1 haploinsufficiency causes developmental and expressive language delay indicating a phenotype distinct from Schinzel-Giedion syndrome. J Med Genet 48, 117-22

Fink M, Wadsak W, Savli M, Stein P, Moser U, Hahn A, Mien LK, Kletter K, Mitterhauser M, Kasper S, Lanzenberger R., 2009. Lateralization of the serotonin-1A receptor distribution in language areas revealed by PET. Neuroimage 45, 598-605.

Flynn, J.M., Deering, W., Goldstein, M., Rahbar, M.H., 1992. Electrophysiological correlates of dyslexic subtypes. JLearn Disabil 25, 133-141.

Freunscht, I., Popp, B., Blank, R., Endele, S., Moog, U., Petri, H., et al., 2013. Behavioral phenotype in five individuals with de novo mutations within the GRIN2B gene. Behav Brain Funct. 9, 20. doi: 10.1186/1744-9081-9-20.

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Gao, J., Wang, W. Y., Mao, Y. W., Gräff, J., Guan, J. S., Pan, L., et al., 2010. A novel pathway regulates memory and plasticity via SIRT1 and miR-134. Nature 466, 1105–9.

Geschwind DH, Rakic P, 2013. Cortical evolution: judge the brain by its cover. Neuron 80, 633-47.

Ghanem, N., Yu, M., Poitras, L., Rubenstein, J. L., Ekker, M., 2008. Characterization of a distinct subpopulation of striatal projection neurons expressing the Dlx genes in the basal ganglia through the activity of the I56ii enhancer. Dev. Biol. 322, 415-424.

Ghashghaei, H. T., Weber, J., Pevny, L., Schmid, R., Schwab, M. H., Lloyd, K. C., et al., 2006.The role of neuregulin-ErbB4 interactions on the proliferation and organization of cells in the subventricular zone. Proc Natl Acad Sci U S A 103, 1930-5.

Gibson, K.M., Christensen, E., Jakobs, C., Fowler, B., Clarke, M.A., Hammersen, G., et al., 1997. The clinical phenotype of succinic semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria): case reports of 23 new patients. Pediatrics 99, 567-74.

Giorgio, E., Vaula, G., Bosco, G., Giacone, S., Mancini, C., Calcia, A., et al., 2015. Two families with novel missense mutations in COL4A1: When diagnosis can be missed. J Neurol Sci 352, 99–104. doi:10.1016/j.jns.2015.03.042.

Goffin, D., Brodkin, E.S., Blendy, J.A., Siegel, S.J., Zhou, Z., 2014. Cellular origins of auditory event-related potential deficits in Rett syndrome. Nat Neurosci 17, 804-806. doi:10.1038/nn.3710.

Gosso, F.M., de Geus, E.J.C., Polderman, T.J.C., Boomsma, D.I., Posthuma, D., Heutink, P., 2007. Exploring the functional role of the CHRM2 gene in human cognition: results from a dense genotyping and brain expression study. BMC Medical Genetics 8, 66.

Goswami, U., Mead, N., Fosker, T., Huss, M., Barnes, L., Leong, V. 2013. Impaired perception of syllable stress in children with dyslexia: a longitudinal study. JMem Lang 69, 1-17. doi:10.1016/j.jml.2013.03.001.

Goucha, T., Zaccarella, E., & Friederici, A.D. 2016. A revival of the homo loquens as a builder of labeled structures: neurocognitive considerations. *Neuroscience & Biobehavioral Reviews* https://doi.org/10.1016/j.neubiorev.2017.01.036.

Guedj, F., Pereira, P.L., Najas, S., Barallobre, M.J., Chabert, C., Souchet, B., et al., 2012. DYRK1A: a master regulatory protein controlling brain growth. Neurobiol Dis 46, 190-203. doi: 10.1016/j.nbd.2012.01.007.

Guo, X., Williams, J.G., Schug, T.T., Li, X., 2010. DYRK1A and DYRK3 promote cell survival through phosphorylation and activation of SIRT1. J Biol Chem 285, 13223-32

Hajós, M., Hoffmann, W. E., Kocsis, B., 2008. Activation of cannabinoid-1 receptors disrupts sensory gating and neuronal oscillation: relevance to schizophrenia. Biol Psychiatry 63, 1075-83.

Hall, M.H., Taylor, G., Sham, P., Schulze, K., Rijsdijk, F., Picchioni, M., et al., 2011. The early auditory gamma-band response is heritable and a putative endophenotype of schizophrenia. Schizophr Bull 37, 778-87.

Hämäläinen, J.A., Rupp, A., Soltész, F., Szücs, D., Goswami, U., 2012. Reduced phase locking to slow amplitude modulation in adults with dyslexia: an MEG study. NeuroImage 59, 2952-2961.

Hämmerle, B., Carnicero, A., Elizalde, C., Ceron, J., Martínez, S., Tejedor, F. J., 2003. Expression patterns and subcellular localization of the Down syndrome candidate protein MNB/DYRK1A suggest a role in late neuronal differentiation. Eur J Neurosci 17, 2277-86.

Hays, S. A., Huber, K. M., Gibson, J.R., 2011. Altered neocortical rhythmic activity states in Fmr1 KO mice are due to enhanced mGluR5 signaling and involve changes in excitatory circuitry.J Neurosci31, 14223-34. doi: 10.1523/JNEUROSCI.3157-11.2011.

bioRxiv preprint doi: https://doi.org/10.1101/114033; this version posted June 14, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Hinna, K. H., Rich, K., Fex-Svenningsen, Å., Benedikz, E., 2015. The rat homolog of the schizophrenia susceptibility gene ZNF804A is highly expressed during brain development, particularly in growth cones. PLoS One 10, e0132456.

Holder, J.L. Jr, Quach, M. M., 2016. The spectrum of epilepsy and electroencephalographic abnormalities due to SHANK3 loss-of-function mutations. Epilepsia 57, 1651-1659. doi: 10.1111/epi.13506.

Homanics GE, DeLorey TM, Firestone LL, Quinlan JJ, Handforth A, Harrison NL, Krasowski MD, Rick CE, Korpi ER, Mäkelä R, Brilliant MH, Hagiwara N, Ferguson C, Snyder K, Olsen RW, 1997. Mice devoid of gamma-aminobutyrate type A receptor beta3 subunit have epilepsy, cleft palate, and hypersensitive behavior. Proc Natl Acad Sci U S A. 94, 4143–4148

Hou, X. J., Ni, K. M., Yang, J. M., Li, X. M., 2014. Neuregulin 1/ErbB4 enhances synchronized oscillations of prefrontal cortex neurons via inhibitory synapses. Neuroscience 261, 107-17.

Hu, C., Chen, W., Myers, S. J., Yuan, H., Traynelis, S. F., 2016. Human GRIN2B variants in neurodevelopmental disorders. J Pharmacol Sci 132, 115-121. doi: 10.1016/j.jphs.2016.10.002.

Huang CH, Pei JC, Luo DZ, Chen C, Chen YW, Lai WS, 2015. Investigation of gene effects and epistatic interactions between Akt1 and neuregulin 1 in the regulation of behavioral phenotypes and social functions in genetic mouse models of schizophrenia. Front Behav Neurosci. 8, 455.

Huang H, Tindall DJ, 2007. Dynamic FoxO transcription factors. J Cell Sci 120, 2479-87.

Huynh TV, Davis AA, Ulrich JD, Holtzman DM, 2017. Apolipoprotein E and Alzheimer's disease: the influence of apolipoprotein E on amyloid-β and other amyloidogenic proteins. J Lipid Res. 58, 824-836.

Jiang YH, Pan Y, Zhu L, Landa L, Yoo J, Spencer C, Lorenzo I, Brilliant M, Noebels J, Beaudet AL, 2010. Altered ultrasonic vocalization and impaired learning and memory in Angelman syndrome mouse model with a large maternal deletion from Ube3a to Gabrb3. PLoS One 5, e12278.

Jiang YH, Pan Y, Zhu L, Landa L, Yoo J, Spencer C, Lorenzo I, Brilliant M, Noebels J, Beaudet AL, 2010. Altered ultrasonic vocalization and impaired learning and memory in Angelman syndrome mouse model with a large maternal deletion from Ube3a to Gabrb3. PLoS One 5, e12278.

Jiménez-Bravo, M., Marrero, V., Benítez-Burraco, A., 2017. An oscillopathic approach to developmental dyslexia: from genes to speech processing. Behav Brain Res 329,84-95.

Jochaut, D., Lehongre, K., Saitovitch, A., Devauchelle, A-D., Olasagasti, I., Chabane, N. et al. 2015. Atypical coordination of cortical oscillations in response to speech in autism. Front. Hum. Neurosci. 9, 171.

Jones, K. A.,Porjesz, B.,Almasy, L.,Bierut, L., Goate, A., Wang, J.C., Dick, D.M., Hinrichs, A., Kwon, J., Rice, J.P., Rohrbaugh, J., Stock, H., Wu, W., Bauer, L.O.,Chorlian, D.B., Crowe, R.R.,Edenberg, H.J.,Foroud, T., Hesselbrock, V.,Kuperman, S.,Nurnberger Jr., J., O'Connor, S.J.,Schuckit, M.A.,Stimus, A.T.,Tischfield, J.A., Reich, T.,Begleiter, H., 2004. Linkage and linkage disequilibrium of evoked EEG oscillations with CHRM2 receptor gene polymorphisms: implications for human brain dynamics and cognition. IntJ Psychophysiol 53, 75-90.

Kameda Y, Saitoh T, Fujimura T, 2011. Hes1 regulates the number and anterior-posterior patterning of mesencephalic dopaminergic neurons at the mid/hindbrain boundary (isthmus). Dev Biol 358, 91-101.

Karam, R.A. Rezk, N.A., Abdelrahman, H.M., Hassan, T.H., Mohammad, D., Hashim, H.M., Fattah, N.R., 2013. Catechol-O-methyltransferase Val158Met polymorphism and

bioRxiv preprint doi: https://doi.org/10.1101/114033; this version posted June 14, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

hyperactivity symptoms in Egyptian children with autism spectrum disorder. Res Dev Disabil 34, 2092-2097.

Kasnauskiene, J., Ciuladaite, Z., Preiksaitiene, E., Utkus, A., Peciulyte, A., Kučinskas, V., 2013.A. new. single. gene. deletion. on. 2q34: ERBB4 is associated with intellectual disability. Am J Med Genet A 161A, 1487-90.

Kaufmann, W. E., Cortell, R., Kau, A. S., Bukelis, I., Tierney, E., Gray, R. M., et al., 2004. Autism spectrum disorder in fragile X syndrome: Communication, social interaction, and specific behaviors. Am J Med Genet A129, 225–234

Kessler, K., Seymour, R.A., Rippon, G., 2016. Brain oscillations and connectivity in autism spectrum disorders (ASD): new approaches to methodology, measurement and modelling. Neurosci Biobehav Rev 71, 601-620.

Ketz, N.A., Jensen, O., & O'Reilly, R.C. (2015). Thalamic pathways underlying prefrontal cortex–medial temporal lobe oscillatory interactions. Trends in Neurosciences, 38(1), 3-12.

Kikuchi, M., Shitamichi, K., Yoshimura, Y., Ueno, S., Hiraishi, H., Hirosawa, T., 2013. Altered brain connectivity in 3-to 7-year-old children with autism spectrum disorder. NeuroImage: Clin2, 394-401.

Kikuchi, Y., Attaheri, A., Wilson, B., Rhone, A.E., Nourski, K.V., et al. 2017 Sequence learning modulates neural responses and oscillatory coupling in human and monkey auditory cortex. *PLOS Biology* 15(4): e2000219. https://doi.org/10.1371/journal.pbio.2000219

Kircher, T., Krug, A., Markov, V., Whitney, C., Krach, S., Zerres, K., et al., 2009.Genetic variation in the schizophrenia-risk gene neuregulin 1 correlates with brain activation and impaired speech production in a verbal fluency task in healthy individuals. Hum Brain Mapp 30, 3406-16.

Ko, J.M., Lim, B.C., Kim, K.J., Hwang, Y.S., Ryu, H.W., Lee, J.H., Kim, J.S., Chae, J.H., 2013. Distinct neurological features in a patient with Schinzel-Giedion syndrome caused by a recurrent SETBP1 mutation. Childs Nerv Syst 29, 525-9. doi: 10.1007/s00381-013-2047-2.

Kocsis, B., 2012. Differential role of NR2A and NR2B subunits in N-methyl-D-aspartate receptor antagonist-induced aberrant cortical gamma oscillations. Biol. Psychiatry 71, 987-95.

Konopka G, Bomar JM, Winden K, Coppola G, Jonsson ZO, Gao F, Peng S, Preuss TM, Wohlschlegel JA, Geschwind DH, 2009. Human-specific transcriptional regulation of CNS development genes by FOXP2. Nature 462, 213-7.

Koolen, D. A., Pfundt, R., Linda, K., Beunders, G., Veenstra-Knol, H. E., Conta, J. H., et al. 2016. The Koolen-de Vries syndrome: a phenotypic comparison of patients with a 17q21.31 microdeletion versus a KANSL1 sequence variant. Eur J Hum Genet 24, 652–659. doi:10.1038/ejhg.2015.178.

Kornilov SA, Rakhlin N, Koposov R, Lee M, Yrigollen C, Caglayan AO, Magnuson JS, Mane S, Chang JT, Grigorenko EL, 2016. Genome-Wide Association and Exome Sequencing Study of language disorder in an isolated population. Pediatrics 137, e20152469.

Kovács, T., Kelemen, O., Kéri, S., 2013. Decreased fragile X mental retardation protein (FMRP) is associated with lower IQ and earlier illness onset in patients with schizophrenia. Psychiatry Res 210, 690-3.

Kovas, Y., & Plomin, R. 2006. Generalist genes: implications for cognitive sciences. *Trends in Cognitive Sciences* 10(5): 198-203.

Krug A, Markov V, Sheldrick A, Krach S, Jansen A, Zerres K, Eggermann T, Stöcker T, Shah NJ, Kircher T, 2009. The effect of the COMT val(158)met polymorphism on neural correlates of semantic verbal fluency. Eur Arch Psychiatry Clin Neurosci 259, 459-65.

bioRxiv preprint doi: https://doi.org/10.1101/114033; this version posted June 14, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Krug, A., Nieratschker, V., Markov, V., Krach, S., Jansen, A., Zerres, K., et al., 2010. Effect of CACNA1C rs1006737 on neural correlates of verbal fluency in healthy individuals. Neuroimage 49, 1831-6.

Kuhlwilm M, Davierwala A, Pääbo S, 2013. Identification of putative target genes of the transcription factor RUNX2. PLoS One 8, e83218.

Kumar, D., Dedic, N., Flachskamm, C., Voulé, S., Deussing, J. M., Kimura, M., 2015. Cacna1c (Cav1.2) modulates electroencephalographic rhythm and rapid eye movement sleep recovery. Sleep 38, 1371-80.

Landi N, Frost SJ, Mencl WE, Preston JL, Jacobsen LK, Lee M, Yrigollen C, Pugh KR, Grigorenko EL, 2013. The COMT Val/Met polymorphism is associated with reading-related skills and consistent patterns of functional neural activation. Dev Sci 16, 13-23.

Lanz, T.A., Guilmette, E., Gosink, M.M., Fischer, J.E., Fitzgerald, L.W., Stephenson, D.T., et al., 2013. Transcriptomic analysis of genetically defined autism candidate genes reveals common mechanisms of action. Mol. Autism 4, 45.

Lehongre, K., Ramus, F., Villiermet, N., Schwartz, D., Giraud, A.-L., 2011. Altered low-gamma sampling in auditory cortex accounts for the three main facets of dyslexia. Neuron 72, 1080-1090.

Lesca, G., Rudolf, G., Labalme, A., Hirsch, E., Arzimanoglou, A., Genton, P., Motte, J., de Saint Martin, A., Valenti, M. P., Boulay, C., De Bellescize, J., Kéo-Kosal, P., Boutry-Kryza, N., Edery, P., Sanlaville, D., Szepetowski, P., 2012. Epileptic encephalopathies of the Landau-Kleffner and continuous spike and waves during slow-wave sleep types: genomic dissection makes the link with autism. Epilepsia53, 1526-38. doi: 10.1111/j.1528-1167.2012.03559.x.

Letinic K, Rakic P, 2001. Telencephalic origin of human thalamic GABAergic neurons. Nature Neurosci 4, 931-6.

Lett, T. A., Kennedy, J.L., Radhu, N., Dominguez, L.G., Chakravarty, M.M., Nazeri, A., Farzan, F., Walter, H., Heinz, A., Mulsant, B.H., Daskalakis, Z.J., Voineskos, A.N., 2016. Prefrontal white matter structure mediates the influence of GAD1 on working memory. Neuropsychopharmacology 41, 2224-31. doi: 10.1038/npp.2016.14.

Li, H., Chou, S. J., Hamasaki, T., Pérez-García, C. G., O'Leary, D. D., 2012. Neuregulin repellent signaling via ErbB4 restricts GABAergic interneurons to migratory paths from ganglionic eminence to cortical destinations. Neural Dev 7, 10.

Li, X. H., Chen, C., Tu, Y., Sun, H. T., Zhao, M. L., Cheng, S. X., et al., 2013. Sirt1 promotes axonogenesis by deacetylation of Akt and inactivation of GSK3. Mol Neurobiol 48, 490-9.

Liang Y, Li Z, Wei J, Li C, Zhang X, Neuroimaging Initiative AD, 2017. Frequency specific effects of ApoE ε4 allele on resting-state networks in nondemented elders. Biomed Res Int 2017, 9823501.

Liao, W., Gandal, M.J., Ehrlichman, R.S., Siegel, S.J., Carlson, G.C., 2012. MeCP2+/- mouse model of RTT reproduces auditory phenotypes associated with Rett syndrome and replicate select EEG endophenotypes of autism spectrum disorder. Neurobiol Dis 46, 88-92.

Lieberman DE, 2008. Speculations about the selective basis for modern human craniofacial form. Evol Anthropol 17, 55-68.

Linkenkaer-Hansen, K., Smit, D.J., Barkil, A., van Beijsterveldt, T.E., Brussaard, A.B., Boomsma, D.I., et al., 2007. Genetic contributions to long-range temporal correlations in ongoing oscillations. J Neurosci 27, 13882-9.

Long, Q, Qiu B, Wang K, Yang J, Jia C, Xin W, Wang P, Han R, Fei Z, Liu W, 2013. Genetically engineered bone marrow mesenchymal stem cells improve functional outcome in a rat model of epilepsy. Brain. Res. 1532, 1-13.

bioRxiv preprint doi: https://doi.org/10.1101/114033; this version posted June 14, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

López-Bendito, G., Cautinat, A., Sánchez, J. A., Bielle, F., Flames, N., Garratt, A. N., et al., 2006. Tangential neuronal migration controls axon guidance: a role for neuregulin-1 in thalamocortical axon navigation. Cell 125, 127-42.

Manoach, D. S., Pan, J. Q., Purcell, S. M., Stickgold, R., 2015. Reduced sleep spindles in schizophrenia: a treatable endophenotype that links risk genes to impaired cognition?Biol. Psychiatry pii: S0006-3223(15)00818-5. doi: 10.1016/j.biopsych.2015.10.003.

Marchese, M., Conti, V., Valvo, G., Moro, F., Muratori, F., Tancredi, R., Santorelli, F. M., Guerrini, R., Sicca, F., 2014. Autism-epilepsy phenotype with macrocephaly suggests PTEN, but not GLIALCAM, genetic screening. BMC Med Genet. 15, 26. doi: 10.1186/1471-2350-15-26.

Marseglia G, Scordo MR, Pescucci C, Nannetti G, Biagini E, Scandurra V, Gerundino F, Magi A, Benelli M, Torricelli F, 2012. 372 kb microdeletion in 18q12.3 causing SETBP1 haploinsufficiency associated with mild mental retardation and expressive speech impairment. Eur J Med Genet 55, 216-21.

Marshall, C. R, Noor, A., Vincent, J. B., Lionel, A.C., Feuk, L., Skaug, J., et al., 2008. Structural variation of chromosomes in autism spectrum disorder. Am J Hum Genet. 82, 477-88. doi: 10.1016/j.ajhg.2007.12.009.

Matsunoshita, Y., Ijiri, K., Ishidou, Y., Nagano, S., Yamamoto, T., Nagao, H., et al., 2011. Suppression of osteosarcoma cell invasion by chemotherapy is mediated by urokinase plasminogen activator activity via up-regulation of EGR1. PLoS One 6, e16234.

Mefford, H. C., Muhle H., Ostertag P., von Spiczak S., Buysse K., Baker, C., et al., 2010. Genome-wide copy number variation in epilepsy: novel susceptibility loci in idiopathic generalized and focal epilepsies. PLoS Genet. 6, e1000962. doi: 10.1371/journal.pgen.1000962.

Miyano, M., Horike, S., Cai, S., Oshimura, M., Kohwi-Shigematsu, T., 2008. DLX5 expression is monoallelic and Dlx5 is up-regulated in the Mecp2-null frontal cortex. J Cell Mol Med 12, 1188-91

Molinaro, N., Lizarazu, M., Lallier, M., Bourguignon, M., Carreiras, M., 2016. Out-of-synchrony speech entrainment in developmental dyslexia. Hum Brain Mapp 37, 2767-2783. doi:10.1002/hbm.23206.

Moran, L.V., Hong, L.E., 2011. High vs low frequency neural oscillations in schizophrenia. Schizophr. Bull. 37, 659-63.

Mori T, Town T, Tan J, Tateishi N, Asano T., 2005. Modulation of astrocytic activation by arundic acid (ONO-2506) mitigates detrimental effects of the apolipoprotein E4 isoform after permanent focal ischemia in apolipoprotein E knock-in mice. J. Cereb Blood Flow Metab 25, 748-62.

Murphy, E., 2015a. Labels, cognomes and cyclic computation: an ethological perspective. Front Psychol 6, 715.

Murphy, E., 2015b. The brain dynamics of linguistic computation. Front Psychol 6, 1515.

Murphy, E., 2016a. The human oscillome and its explanatory potential. Biolinguistics 10, 6-20.

Murphy, E., 2016b. A theta-gamma neural code for feature set composition with phase-entrained delta nestings. UCL Working Papers in Linguistics 28: 1-23.

Murphy, E., Benítez-Burraco, A., 2016a. Bridging the gap between genes and language deficits in schizophrenia: an oscillopathic approach. Front Hum Neurosci 10, 422.

Murphy, E., Benítez-Burraco, A., 2016b. Language deficits in schizophrenia and autism as related oscillatory connectomophathies: an evolutionary account. Neurosci Biobehav Rev S0149-7634(16)30155-5.

Nagamani, S.C., Erez, A., Ben-Zeev, B., Frydman, M., Winter, S., Zeller, R., El-Khechen, D., Escobar, L., Stankiewicz, P., Patel, A., Cheung, S.W., 2013. Detection of copy-number

bioRxiv preprint doi: https://doi.org/10.1101/114033; this version posted June 14, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

variation in AUTS2 gene by targeted exonic array CGH in patients with developmental delay and autistic spectrum disorders. Eur J Hum Genet 21, 343-6. doi: 10.1038/ejhg.2012.157.

Nakamura, T., Matsumoto, J., Takamura, Y., Ishii, Y., Sasahara, M., Ono, T, et al., 2015. Relationships among parvalbumin-immunoreactive neuron density, phase-locked gamma oscillations, and autistic/schizophrenic symptoms in PDGFR-β knock-out and control mice. PLoS One 10, e0119258.

Namiki, K., Nakamura, A., Furuya, M., Mizuhashi, S., Matsuo, Y., Tokuhara, N., et al., 2007. Involvement of p38alpha in kainate-induced seizure and neuronal cell damage. J. Recept. Signal Transduct. Res 27, 99-111.

Naqvi, S., Cole, T. y Graham, J. M., Jr., 2000. Cole-Hughes macrocephaly syndrome and associated autistic manifestations. Am J Med Genet 94, 149-152.

Newell, K. A., Karl, T., Huang, X. F., 2013. A neuregulin. 1 transmembrane domain mutation causes imbalanced glutamatergic and dopaminergic receptor expression in mice. Neuroscience. 248, 670-80.

Nguyen, P. T., Nakamura, T., Hori, E., Urakawa, S., Uwano, T., Zhao, J., et al., 2011. Cognitive and socio-emotional deficits in platelet-derived growth factor receptor-β gene knockout mice. PLoS One 6, e18004.

Nicodemus, K. K., Elvevåg, B., Foltz, P. W., Rosenstein, M., Diaz-Asper, C., Weinberger, D. R. (2014). Category fluency, latent semantic analysis and schizophrenia: a candidate gene approach. Cortex 55, 182-91.

O'Roak, B. J., Deriziotis, P., Lee, C., Vives, L., Schwartz, J. J., Girirajan, S., Karakoc, E., Mackenzie, A. P., Ng, S. B., Baker, C., Rieder, M. J., Nickerson, D. A., Bernier, R., Fisher, S. E., Shendure, J., Eichler, E. E., 2011. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. Nat Genet. 43, 585-9. doi: 10.1038/ng.835.

Ogawa, S., Kwon, C.-H., Zhou, J., Koovakkattu, D., Parada, L. F., Sinton, C., 2007. A seizure-prone phenotype is associated with altered free-running rhythm in Pten mutant mice. Brain Res. 1168, 112–123. doi: 10.1016/j.brainres.2007.06.074.

Osbun, N., Li, J., O'Driscoll, M.C., Strominger, Z., Wakahiro, M., Rider, E., et al., 2011. Genetic and functional analyses identify DISC1 as a novel callosal agenesis candidate gene. Am J Med Genet A 155A, 1865-76.

Page, D. T., Kuti, O. J., Prestia, C., Sur, M., 2009. Haploinsufficiency for Pten and serotonin transporter cooperatively influences brain size and social behavior. Proc Natl Acad Sci U S A106, 1989–1994. doi: 10.1073/pnas.0804428106.

Pal, D. K., Li, W., Clarke, T., Lieberman, P., Strug, L. J., 2010. Pleiotropic effects of the 11p13 locus on developmental verbal dyspraxia and EEG centrotemporal sharp waves. Genes Brain Behav9, 1004-12.

Palo OM, Antila M, Silander K, Hennah W, Kilpinen H, Soronen P, Tuulio-Henriksson A, Kieseppä T, Partonen T, Lönnqvist J, Peltonen L, Paunio T., 2007. Association of distinct allelic haplotypes of DISC1 with psychotic and bipolar spectrum disorders and with underlying cognitive impairments. Hum Mol Genet 16, 2517–2528

Paluszkiewicz, S. M., Olmos-Serrano, J. L., Corbin, J. G., Huntsman, M. M., 2011. Impaired inhibitory control of cortical synchronization in fragile X syndrome. J Neurophysiol 106, 2264-72. doi: 10.1152/jn.00421.2011.

Paracchini, S., Diaz, R., Stein, J., 2016. Advances in dyslexia genetics—new insights into the role of brain asymmetries, in: Friedmann, T., Dunlap, J. C., Goodwin, S. F. (Eds.), Advances in Genetics 96. Academic Press: London, pp. 53–97. doi:10.1016/bs.adgen.2016.08.003.

Pearl, P. L., Novotny, E. J., Acosta, M. T., Jakobs, C., Gibson, K. M., 2003. Succinic semialdehyde dehydrogenase deficiency in children and adults. Ann Neurol. 54 Suppl 6, S73-80.

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Perovic, A., Janke, V., 2013. Issues in the acquisition of binding, control and raising in high-functioning children with autism. UCL Work. Papers in Linguistics 25, 131–143.

Perovic, A., Modyanova, N., Wexler, K., 2007. Knowledge of c-command and A-movement in children and adolescents with autism and with Asperger syndrome. Paper presented at GALA 2007: Generative Approaches to Language Acquisition, Barcelona, 6–8 September.

Peters, S.U., Gordon, R.L., Key, A.P., 2015. Induced gamma oscillations differentiate familiar and novel voices in children with MECP2 duplication and Rett syndromes. J Child Neurol 30, 145-52.

Pettigrew, K.A., Frinton, E., Nudel, R., Chan, M.T., Thompson, P., Hayiou-Thomas, M.E., Talcott, J.B., Stein, J., Monaco, A.P., Hulme, C., Snowling, M.J., Newbury, D.F., Paracchini, S., 2016. Further evidence for a parent-of-origin effect at the NOP9 locus on language-related phenotypes. J Neurodev Disord. 8, 24. doi: 10.1186/s11689-016-9157-6.

Pietiläinen OP, Paunio T, Loukola A, Tuulio-Henriksson A, Kieseppä T, Thompson P, Toga AW, van Erp TG, Silventoinen K, Soronen P, Hennah W, Turunen JA, Wedenoja J, Palo OM, Silander K, Lönnqvist J, Kaprio J, Cannon TD, Peltonen L., 2009. Association of AKT1 with verbal learning, verbal memory, and regional cortical gray matter density in twins. Am J Med Genet B Neuropsychiatr Genet 150B, 683-92

Pignatelli M, Beyeler A, Leinekugel X, 2012. Neural circuits underlying the generation of theta oscillations. J Physiol Paris 106, 81-92.

Pleasure, S. J., Anderson, S., Hevner, R., Bagri, A., Marin, O., Lowenstein, D. H., et al. 2000. Cell migration from the ganglionic eminences is required for the development of hippocampal GABAergic interneurons. Neuron 28, 727-40.

Plomin, R., & Kovas, Y. 2005. Generalist genes and learning disabilities. *Psychological Bulletin* 131(4): 592-617.

Poelmans, G., Buitelaar, J. K., Pauls, D. L., Franke, B., 2011. A theoretical molecular network for dyslexia: integrating available genetic findings. Mol Psychiatry 16,365-82.

Poeppel, D., 2012. The maps problem and the mapping problem: Two challenges for a cognitive neuroscience of speech and language. Cogn. Neuropsychol. 29, 34–55. doi:10.1080/02643294.2012.710600.

Poitras, L., Yu, M., Lesage-Pelletier, C., Macdonald, R. B., Gagné, J. P., Hatch, G., Kelly, I., Hamilton, S. P., Rubenstein, J. L., Poirier, G. G., Ekker, M., 2010. An SNP in an ultraconserved regulatory element affects Dlx5/Dlx6 regulation in the forebrain. Development 137, 3089-3097

Poot, M., van't Slot, R., Leupert, R., Beyer, V., Passarge, E., Haaf, T., 2009. Three de novo losses and one insertion within a pericentric inversion of chromosome 6 in a patient with complete absence of expressive speech and reduced pain perception. Med Genet 52, 27-30.

Provenzano, G., Sgadò, P., Genovesi, S., Zunino, G., Casarosa, S., Bozzi, Y., 2015. Hippocampal dysregulation of FMRP/mGluR5 signaling in engrailed-2 knockout mice: a model of autism spectrum disorders. Neuroreport 26, 1101-5. doi: 10.1097/WNR.0000000000000477.

Pun, R.Y., Rolle, I.J., Lasarge, C.L., Hosford, B.E., Rosen, J.M., Uhl, J.D. et al., 2012. Excessive activation of mTOR in postnatally generated granule cells is sufficient to cause epilepsy. Neuron 75, 1022-34.

Radwan, B., Dvorak, D., Fenton, A.A., 2016. Impaired cognitive discrimination and discoordination of coupled theta-gamma oscillations in Fmr1 knockout mice. Neurobiol Dis 88, 125-38. doi: 10.1016/j.nbd.2016.01.003.

Rakhade, S.N., Shah, A.K., Agarwal, R., Yao, B., Asano, E., Loeb, J.A., 2007. Activity-dependent gene expression correlates with interictal spiking in human neocortical epilepsy. Epilepsia 48 Suppl 5, 86-95.

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Rakic P, 2009. Evolution of the neocortex: a perspective from developmental biology. Nature Rev Neurosci 10, 724–35.

Rogalski E, Weintraub S, Mesulam MM, 2013. Are there susceptibility factors for primary progressive aphasia? Brain Lang 127, 135-8.

Rogers JT, Morganti JM, Bachstetter AD, Hudson CE, Peters MM, Grimmig BA, Weeber EJ, Bickford PC, Gemma C., 2011. CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity. J Neurosci 31, 16241-50.

Rojas, D.C., Maharajh, K., Teale, P., Rogers, S.J., 2008. Reduced neural synchronization of gamma-band MEG oscillations in first-degree relatives of children with autism. BMC Psychiatry 8, 66.

Roll, P., Rudolf, G., Pereira, S., Royer, B., Scheffer, I. E., Massacrier, A., et al., 2006. SRPX2 mutations in disorders of language cortex and cognition. Hum Mol Genet 15, 1195-207.

Roll, P., Vernes, S. C., Bruneau, N., Cillario, J., Ponsole-Lenfant, M., Massacrier, A., et al., 2010. Molecular networks implicated in speech-related disorders: FOXP2 regulates the SRPX2/uPAR complex. Hum. Mol. Genet. 19, 4848-60.

Rolstad, S., Pålsson, E., Ekman, C.J., Eriksson, E., Sellgren, C.,Landén, M., 2015. Polymorphisms of dopamine pathway genes NRG1 and LMX1A are associated with cognitive performance in bipolar disorder. Bipolar Disord 17, 859-68.

Roy SM, Grum-Tokars VL, Schavocky JP, Saeed F, Staniszewski A, Teich AF, Arancio O, Bachstetter AD, Webster SJ, Van Eldik LJ, Minasov G, Anderson WF, Pelletier JC, Watterson DM, 2015. Targeting human central nervous system protein kinases: An isoform selective p38αMAPK inhibitor that attenuates disease progression in Alzheimer's disease mouse models. ACS Chem Neurosci 6, 666-80.

Royer-Zemmour, B., Ponsole-Lenfant, M., Gara, H., Roll, P., Lévêque, C., Massacrier, A., et al., 2008. Epileptic and developmental disorders of the speech cortex: ligand/receptor interaction of wild-type and mutant SRPX2 with the plasminogen activator receptor uPAR. Hum Mol Genet 17, 3617-30.

Ruiz-Mejias, M., Martinez de Lagran, M., Mattia, M., Castano-Prat, P., Perez-Mendez, L., Ciria-Suarez, L. et al., 2016. Overexpression of Dyrk1A, a Down syndrome candidate, decreases excitability and impairs gamma oscillations in the prefrontal cortex. J Neurosci 36, 3648-59.

Saalmann, Y. B., Pinsk, M. A., Wang, L., Li, X., Kastner, S, 2012. The pulvinar regulates information transmission between cortical areas based on attention demands. Science 337, 753-756.

Saharan, S., Jhaveri, D. J., Bartlett, P. F., 2013. SIRT1 regulates the neurogenic potential of neural precursors in the adult subventricular zone and hippocampus. J Neurosci Res 91, 642-59.

Sakakibara, A., Horwitz, A. F., 2006. Mechanism of polarized protrusion formation on neuronal precursors migrating in the developing chicken cerebellum. J Cell Sci 119, 3583-92.

Sandhu, K.V., Lang, D., Müller, B., Nullmeier, S., Yanagawa, Y., Schwegler, H., Stork, O., 2014. Glutamic acid decarboxylase 67 haplodeficiency impairs social behavior in mice. Genes Brain Behav 13, 439-50. doi: 10.1111/gbb.12131.

Schutte SS., Schutte RJ., Barragan EV., O'Dowd DK. (2016) Model systems for studying cellular mechanisms of SCN1A-related epilepsy. J Neurophysiol. 115(4):1755-66. doi: 10.1152/jn.00824.2015.

Seshadri S., Kamiya A., Yokota Y., Prikulis I., Kano S., Hayashi-Takagi A., Stanco A., Eom TY., Rao S., Ishizuka K., Wong P., Korth C., Anton ES., Sawa A., 2010. Disrupted-in-Schizophrenia-1 expression is regulated by beta-site amyloid precursor protein cleaving

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enzyme-1-neuregulin cascade. Proc Natl Acad Sci U S A. 107, 5622-7. doi: 10.1073/pnas.0909284107.

Seshadri, S., Faust, T., Ishizuka, K., Delevich, K., Chung, Y., Kim, S. H., et al., 2015. Interneuronal DISC1 regulates NRG1-ErbB4 signalling and excitatory-inhibitory synapse formation in the mature cortex. Nat. Commun. 6, 10118.

Singer W, 2013. Cortical dynamics revisited. Trends Cogn Sci 17, 616-26.

Smigiel, R., Cabala, M., Jakubiak, A., Kodera, H., Sasiadek, M. J., Matsumoto, N., et al., 2016. Novel COL4A1 mutation in an infant with severe dysmorphic syndrome with schizencephaly, periventricular calcifications, and cataract resembling congenital infection. Birth Defects Res Part A Clin Mol Teratol 106, 304–307. doi:10.1002/bdra.23488.

Smith, L. E., Barker, E. T., Seltzer, M. M., Abbeduto, L., Greenberg, J. S., 2012. Behavioral phenotype of fragile X syndrome in adolescence and adulthood. Am J Intellect Dev Disabil 117, 1-17.

Soeiro-De-Souza MG, Bio DS, David DP, Missio G, Lima B, Fernandes F, Machado-Vieira R, Moreno RA., 2013. Gender effects of the COMT Val 158 Met genotype on verbal fluency in healthy adults. Mol Med Rep 8, 837-44

Soltész, F., Szücs, D., Leong, V., White, S., Goswami, U., Ziegler, J., et al., 2013. Differential entrainment of neuroelectric delta oscillations in developmental dyslexia. PLoS One 8, e76608. doi:10.1371/journal.pone.0076608.

Soorya, L., Kolevzon, A., Zweifach, J., Lim, T., Dobry, Y., Schwartz, L., et al., 2013. Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and SHANK3 deficiency. Mol Autism 4, 18. doi: 10.1186/2040-2392-4-18.

Souchet, B., Guedj, F., Sahún, I., Duchon, A., Daubigney, F., Badel, A., et al., 2014. Excitation/inhibition balance and learning are modified by Dyrk1a gene dosage. Neurobiol Dis 69, 65-75.

Striedter GF, 2005. Principles of Brain Evolution. Sunderland, MA: Sinauer Associates,

Strug, L.J., Clarke, T., Chiang, T., Chien, M., Baskurt, Z., Li, W., et al., 2009. Centrotemporal sharp wave EEG trait in rolandic epilepsy maps to Elongator Protein Complex 4 (ELP4). Eur J Hum Genet17, 1171-81.

Suárez-Pinilla, P., Roiz-Santiañez, R., Ortiz-García de la Foz, V., Guest, P. C., Ayesa-Arriola, R., Córdova-Palomera, A., et al., 2015. Brain structural and clinical changes after first episode psychosis: Focus on cannabinoid receptor 1 polymorphisms. Psychiatry Res 233, 112-9.

Sugiura L, Toyota T, Matsuba-Kurita H, Iwayama Y, Mazuka R, Yoshikawa T, Hagiwara H, 2017. Age-dependent effects of Catechol-O-Methyltransferase (COMT) gene Val158Met polymorphism on language function in developing children. Cereb Cortex 27, 104-116.

Sundvall, M., Veikkolainen, V., Kurppa, K., Salah, Z., Tvorogov, D., van Zoelen, E. J., et al., 2010. Cell death or survival promoted by alternative isoforms of ErbB4. Mol Biol Cell 21, 4275-86. doi: 10.1091/mbc.E10-04-0332.

Szklarczyk, D., Franceschini, A., Wyder, S., Forslund, K., Heller, D., Huerta-Cepas, J., et al., 2015. STRING v10: protein-protein interaction networks, integrated over the tree of life. Nucleic Acids Res. 43, D447-52.

Tager-Flusberg, H., Paul, R., Lord, C.E., 2005. Language and communication in autism, in: Volkmar, F., Paul, R., Klin, A., Cohen, D. J. (Eds.), Handbook of Autism and Pervasive Developmental Disorders: Vol. 1. Diagnosis, Development, Neurobiology, and Behavior, New York, Wiley, pp. 335-364.

Talkowski, M.E, Mullegama, S.V,, Rosenfeld, J.A,, van Bon, B.W., Shen, Y., Repnikova, E.A., et al., 2011. Assessment of 2q23.1 microdeletion syndrome implicates MBD5 as a single causal locus of intellectual disability, epilepsy, and autism spectrum disorder. Am J Hum Genet 89, 551-63.doi: 10.1016/j.ajhg.2011.09.011.

bioRxiv preprint doi: https://doi.org/10.1101/114033; this version posted June 14, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Tan HY, Chen AG, Chen Q, Browne LB, Verchinski B, Kolachana B, Zhang F, Apud J, Callicott JH, Mattay VS, Weinberger DR, 2012. Epistatic interactions of AKT1 on human medial temporal lobe biology and pharmacogenetic implications. Mol Psychiatry 17, 1007-16.

Tan HY, Chen AG, Kolachana B, Apud JA, Mattay VS, Callicott JH, Chen Q, Weinberger DR., 2012. Effective connectivity of AKT1-mediated dopaminergic working memory networks and pharmacogenetics of anti-dopaminergic treatment. Brain 135, 1436-45.

Theyel, B., Llano, D., Sherman, S, 2009. The corticothalamocortical circuit drives higher-order cortex in the mouse. Nature Neurosci 13, 84-88

Thomson PA, Parla JS, McRae AF, Kramer M, Ramakrishnan K, Yao J, Soares DC, McCarthy S, Morris SW, Cardone L, Cass S, Ghiban E, Hennah W, Evans KL, Rebolini D, Millar JK, Harris SE, Starr JM, MacIntyre DJ; Generation Scotland, McIntosh AM, Watson JD, Deary IJ, Visscher PM, Blackwood DH, McCombie WR, Porteous DJ, 2014. 708 common and 2010 rare DISC1 locus variants identified in 1542 subjects: analysis for association with psychiatric disorder and cognitive traits. Mol Psychiatry 19, 668-75.

Tierney, A. L., Gabard-Durnam, L., Vogel-Farley, V., Tager-Flusberg, H., Nelson, C. A., 2012. Developmental trajectories of resting EEG power: An endophenotype of autism spectrum disorder. PLoS One 7, e39127.

Tilot, A.K., Frazier, T.W. 2nd, Eng, C., 2015. Balancing proliferation and connectivity in PTEN-associated autism spectrum disorder. Neurotherapeutics 12, 609-19. doi: 10.1007/s13311-015-0356-8.

Tosato, S., Bellani, M., Bonetto, C., Ruggeri, M., Perlini, C., Lasalvia, A., et al., 2012. Is neuregulin 1 involved in determining cerebral volumes in schizophrenia? Preliminary results showing a decrease in superior temporal gyrus volume. Neuropsychobiology 65, 119-25. doi: 10.1159/000330584.

Turner SJ, Brown A, Arpone M, Anderson V, Morgan AT, Scheffer IE, 2017. Dysarthria and broader motor speech deficits in Dravet syndrome. Neurology 88, 743-749

Uchino, J., Suzuki, M., Hoshino, K., Nomura, Y., Segawa, M., 2001. Development of language in Rett syndrome. Brain Dev 23, S233-S235.

Uhlhaas, P. J., Roux, F., Singer W, 2013. Thalamocortical synchronization and cognition: implications for schizophrenia? Neuron 77, 997–999.

Uhlhaas, P.J., Haenschel, C., Nikolic, D., Singer, W., 2008. The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia. Schizophr Bull 34, 927–943.

Urak, L., Feucht, M., Fathi, N., Hornik, K., Fuchs, K., 2006. A GABRB3 promoter haplotype associated with childhood absence epilepsy impairs transcriptional activity. Hum Mol Genet15, 2533-41.

Van Beijsterveldt, C.E., Molenaar, P.C., de Geus, E.J., Boomsma, D.I., 1996. Heritability of human brain functioning as assessed by electroencephalography. Am J Hum Genet 58, 562–573.

Van Bon, B. W., Balciuniene, J., Fruhman, G., Nagamani, S. C., Broome, D. L., Cameron, E., et al., 2011. The. phenotype. of. recurrent. 10q22q23 deletions and duplications. Eur J Hum Genet 19, 400-8.

Veenstra-VanderWeele, J., Cook, E. H., 2004. Molecular genetics of autism spectrum disorder. Mol Psychiatry 9, 819-832.

Vertes RP, Kocsis B, 1997. Brainstem-diencephalo-septohippocampal systems controlling the theta rhythm of the hippocampus. Neuroscience 81, 893-926.

Veyrac, A., Besnard, A., Caboche, J., Davis, S., Laroche, S., 2014. The transcription factor Zif268/Egr1, brain plasticity, and memory. Prog Mol Biol Transl Sci122, 89-129.

bioRxiv preprint doi: https://doi.org/10.1101/114033; this version posted June 14, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Vosskuhl, J., Huster, R.J., & Herrmann, C.S. 2015. Increase in short-term memory capacity induced by down-regulating individual theta frequency via transcranial alternating current stimulation. *Frontiers Human Neuroscience* 9: 257. doi: 10.3389/fnhum.2015.00257.

Wada, R., 2015. Clinician recasts and production of complex syntax by children with and without specific language impairment. All Graduate Theses and Dissertations. Paper 4277.

Wahl, M., Marzinzik, F., Friederici, A. D., Hahne, A., Kupsch, A., Schneider, G. H., Saddy, D., Curio, G., Klostermann, F, 2008. The human thalamus processes syntactic and semantic language violations. Neuron 59, 695-707.

Walker RM, Hill AE, Newman AC, Hamilton G, Torrance HS, Anderson SM, Ogawa F, Derizioti P, Nicod J, Vernes SC, Fisher SE, Thomson PA, Porteous DJ, Evans KL, 2012. The DISC1 promoter: characterization and regulation by FOXP2. Hum Mol Genet 21, 2862-72.

Wang, D,. Li, Z., Zhang, Y., Wang, G., Wei, M., Hu, Y., et al., 2016. Targeting of microRNA-199a-5p protects against pilocarpine-induced status epilepticus and seizure damage via SIRT1-p53 cascade. Epilepsia 57, 706-16. doi: 10.1111/epi.13348.

Weiss, L. A., Escayg, A., Kearney, J. A., Trudeau, M., MacDonald, B. T., Mori, M., et al., 2003. Sodium channels SCN1A, SCN2A and SCN3A in familial autism. Mol Psychiatry 8, 186-94.

Whitman, J. C., Ward, L. M., Woodward, T.S, 2013. Patterns of cortical oscillations organize neural activity into whole-brain functional networks evident in the fMRI BOLD signal. Front Hum Neurosci 7, 80.

Wilkinson, C., & Murphy, E. 2016. Joint interventions in autism spectrum disorder: relating oscillopathies and syntactic deficits. *UCL Working Papers in Linguistics* 28: 1-7.

Williams, S. R., Mullegama, S. V., Rosenfeld, J. A., Dagli, A. I., Hatchwell, E., Allen, W. P., Williams, C. A., Elsea, S. H., 2010. Haploinsufficiency of MBD5 associated with a syndrome involving microcephaly, intellectual disabilities, severe speech impairment, and seizures. Eur J Hum Genet 18, 436-41. doi: 10.1038/ejhg.2009.199.

Wilsch, A., Henry, M.J., Herrmann, B., Maess, B., & Obleser, J. (2015). Alpha oscillatory dynamics index temporal expectation benefits in working memory. *Cerebral Cortex* 25(7): 1938-1946.

Wojtecki, L., Elben, S., Vesper, J., & Schnitzler, A. (2016). The rhythm of the executive gate of speech: subthalamic low-frequency oscillations increase during verbal generation. *European Journal of Neuroscience* doi: 10.1111/ejn.13429.

Wöstmann, M., Herrmann, B., Wilsch, A., & Obleser, J. (2015). Neural alpha dynamics in younger and older listeners reflect acoustic challenges and predictive benefits. Journal of *Neuroscience* 35(4): 1458-1467.

Xiong H, Dai M, Ou Y, Pang J, Yang H, Huang Q, Chen S, Zhang Z, Xu Y, Cai Y, Liang M, Zhang X, Lai L, Zheng Y, 2014. SIRT1 expression in the cochlea and auditory cortex of a mouse model of age-related hearing loss. Exp Gerontol 51, 8-14.

Xu, T., Stephane, M., Parhi, K.K., 2012. Selection of abnormal neural oscillation patterns associated with sentence-level language disorder in schizophrenia. Conf Proc IEEE Eng Med Biol Soc 4923-6. doi: 10.1109/EMBC.2012.6347098.

Xu, T., Stephane, M., Parhi, K.K., 2013. Multidimensional analysis of the abnormal neural oscillations associated with lexical processing in schizophrenia. Clin EEG Neurosci 44, 135-143.

Yu, W., De Hert, M., Moons, T., Claes, S. J., Correll, C. U., van Winkel, R., 2013. CNR1 gene and risk of the metabolic syndrome in patients with schizophrenia. J Clin Psycopharmacol 33, 186-92. doi: 10.1097/JCP.0b013e318283925e.

Zhan, Y., 2015. Theta frequency prefrontal-hippocampal driving relationship during free exploration in mice. Neuroscience 300, 554-65. doi: 10.1016/j.neuroscience.2015.05.063.

bioRxiv preprint doi: https://doi.org/10.1101/114033; this version posted June 14, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Zhan, Y., Paolicelli, R.C., Sforazzini, F., Weinhard, L., Bolasco, G., Pagani, F., Vyssotski, A.L., Bifone, A., Gozzi, A., Ragozzino, D., Gross, C.T., 2014. Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. Nat Neurosci 17, 400-406.

Zhang Z, Zhang W, Huang S, Sun Q, Wang Y, Hu Y, Sun N, Zhang Y, Jiang Z, Minato N, Pin JP, Su L, Liu J, 2015. GABAB receptor promotes its own surface expression by recruiting a Rap1-dependent signaling cascade. J Cell Sci 128, 2302-13.

Zheng, F., Wang, L., Jia, M., Yue, W., Ruan, Y., Lu, T. et al., 2011. Evidence for association between Disrupted-in-Schizophrenia 1 (DISC1) gene polymorphisms and autism in Chinese Han population: a family-based association study. Behav Brain Funct 7, 14.