bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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 The copyright holder for this preprint (which was not certified by peer review) is the author/funder.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.

Full title: Schizophrenia and human self-domestication: an evolutionary linguistics approach
Short title (to be used as running head): Schizophrenia and human-self domestication

Antonio Benítez-Burraco[1*], Lorena Di Pietro[2], Marta Barba[2], and Wanda Lattanzi[2]

1. Department of Philology, University of Huelva, Huelva, Spain
2. Institute of Anatomy and Cell Biology, Università Cattolica del Sacro Cuore, Rome, Italy

Keywords: schizophrenia, domestication, neural crest, language impairment, language evolution, candidate genes, gene expression profile.

Number of tables: 1
Number of figures: 4

* Corresponding author
Antonio Benítez Burraco
Departamento de Filología
Facultad de Humanidades
Campus de "El Carmen"
Universidad de Huelva
Avda. de las Fuerzas Armadas s/n
21071-Huelva (Spain)
Telephone number: 0034 959 219 113
Email: antonio.benitez@dfesp.uhu.es

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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 The copyright holder for this preprint (which was not certified by peer review) is the author/funder.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.

Abstract

Schizophrenia (SZ) is a pervasive neurodevelopmental disorder entailing social and cognitive deficits, including marked problems with language. Its complex multifactorial etiopathogenesis, including genetic and environmental factors, is still widely uncertain. SZ incidence has always been high and quite stable in human populations, across time and regardless of cultural implications, due to unclear reasons. It has been hypothesised that SZ pathophysiology may involve the biological components that changed during the recent human evolutionary history and led to our distinctive mode of cognition, which includes language skills. In this paper we explore this possibility, focusing on the self-domestication of the human species. This has been claimed to account for many human-specific distinctive traits, including aspects of our behaviour and cognition, and to favour the emergence of complex languages through cultural evolution. The "domestication syndrome" in mammals comprises the constellation of traits exhibited by domesticated strains, seemingly resulting from the hypofunction of the neural crest. It is our intention to show that people with SZ exhibit more marked domesticated traits at the morphological, physiological, and behavioural levels. We also show that genes involved in domestication and neural crest development and function comprise nearly 20% SZ candidates, most of which exhibit altered expression profiles in the brain of SZ patients, specifically in areas involved in language processing. Based on these observations, we conclude that SZ may represent an abnormal ontogenetic itinerary for the human faculty of language, resulting, at least in part, from changes in genes important for the "domestication syndrome" and, primarily involving the neural crest.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

1. Introduction

Schizophrenia (SZ) is a pervasive neurodevelopmental condition entailing different and severe social and cognitive deficits. Core distinctive symptoms of SZ include delusions, hallucinations, impaired motivation, reduction in spontaneous speech, and social withdrawal; cognitive impairment, episodes of elated mood, and episodes of depressive mood are also commonly observed (van Os and Kapur 2009, Owen et al., 2016). SZ prevalence has been found stable across time and cultures, to the extent that it has been considered a human-specific disease. Indeed, susceptibility genes are poorly conserved across species, some of them being absent in great apes (Brüne, 2004, Pearlson and Folley, 2008). Also, most of the biological components that seem to have played a central role in the evolution of human cognition are found impaired in SZ patients. For instance, after our split from great apes, the frontal cortical circuitry was remodelled; this circuitry is responsible for many human-specific cognitive abilities and is found dysfunctional in patients with SZ and other psychiatric conditions (Teffer and Semendeferi, 2012). Likewise, genomic regions that have undergone positive selection in anatomically-modern humans (AMHs) are enriched in gene loci associated with SZ (Srinivasan et al., 2016). This enrichment has been recently linked to functional elements like introns and untranslated regions (Srinivasan et al., 2017). This rises the intriguing possibility that most of SZ risk alleles appeared more recently in human evolution. Overall, these evidences suggest that the evolutionary changes occurred in the human lineage, particularly after the split from extinct hominins, may help clarifying some aspects of SZ. On the other hand, delving into the SZ polygenic etiopathogenesis, which acts synergistically with unclear environmental factors, might help understand the changes that brought about our human distinctive cognitive phenotype, including our language abilities.

Language deficits are a hallmark of SZ, which has been defined as “the price that homo sapiens pays for language” (Crow, 2000). These usually manifest as problems in speech perception (in the form of auditory verbal hallucinations), abnormal speech production (known as Formal Thought Disorder, FTD), and production of abnormal linguistic content (that is, delusions) (Stephane et al., 2007, and 2014). These major positive symptoms can be reduced to disturbances in linguistic computation (Hinzen and Roselló 2015) that result from atypical brain development and wiring during growth (Li et al., 2009, and 2012). In our previous work we have showed that this abnormal mode of processing language can be specifically drawn back to an abnormal, distinctive oscillatory profile of the brain during language computation (Murphy and Benítez-Burraco, 2016a). Also, we have showed that candidates for SZ are overrepresented among the genes believed to be involved in the evolution of our language-readiness, that is, our species-specific ability to learn and use languages (Boeckx and Benítez-Burraco, 2014a, 2014b; Benítez-Burraco and Boeckx, 2015, Murphy and Benítez-Burraco, 2016a).

Besides the genomic and epigenomic changes that favoured our speciation, we expect that our cognitive phenotype was also modelled by changes occurred later, during our self-domestication (Benítez-Burraco et al., 2016a). The idea of human beings as domesticated primates can be drawn back to Darwin (1871). Recent comparisons with extinct hominins have revealed that AMHs exhibit a number of domesticated traits, including differences in the brain and the face, changes in dentition, reduction of aggressiveness, and retention of juvenile characteristics (see Thomas, 2014 for details). Many authors have argued that the relaxation of the selective pressures on our species resulting from this process of self-domestication may have contributed to the creation of the cultural niche that favoured the emergence of modern languages (Hare and Tomasello, 2005, Deacon, 2009, Thomas, 2014, among others). This

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

niche provides humans with an extended socialization window, enabling them to receive a greater amount of linguistic stimuli, to involve in enhanced and prolonged communication exchanges with other conspecifics, and to experiment with language for a longer time. In particular, language complexity is expected to increase in these comfortable conditions, as attested by domestic strains of songbirds, in which domestication triggers variation and complexity in their songs (Takahasi and Okanoya, 2010, Kagawa et al., 2012). Importantly, this possibility is supported by several linguistic studies revealing positive correlations between aspects of linguistic complexity and aspects of social complexity (Wray and Grace, 2007, Lupyan and Dale, 2010), or pointing out to the emergent nature of core properties of human languages, resulting from cultural transmission (Benítez-Burraco, 2016).

Several selectionist accounts of why humans became self-domesticated have been posited over time, ranging from selection against aggression and towards social tolerance, to a by-product of mate-choices, to adaptation to the human-made environment (Thomas, 2014). In our recent work we have hypothesised that self-domestication might be (also) a by-product of the changes that brought about our more globular skull/brain and our language-readiness (Benítez-Burraco et al., 2016a). The reason is that candidates for globularization and language-readiness are found among (and interact with) the genes believed important for the development and function of the neural crest (NC). And as noted by Wilkins et al (2014), the set of traits observed in domestic mammals, ranging from changes in the craniofacial region, to changes in the skin, the reproductive and vital cycles, and behaviour (the so-called 'domestication syndrome"), may result from the hypofunction of the NC, in turn triggered by the selection for tameness (see Sánchez-Villagra et al., 2016, for a recent account).

Building on this hypothesis, in our previous work we have showed that the complex pathophysiology of some human cognitive diseases entailing problems with language can be, at least in part, linked to an abnormal presentation of the "domestication syndrome" (Murphy and Benítez-Burraco, 2016a). Specifically, we have discussed how patients suffering from autism spectrum disorders (ASD) exhibit a plethora of distinctive behavioural, neurological, and physical anomalies, including dysmorphic features, that seem to be opposite as the "domesticated" traits observed in typically-developing (TD) individuals (Benítez-Burraco et al., 2016b).

Interestingly, ASD and SZ have been hypothesised to be opposite poles in the continuum of cognitive modes, encompassing also the TD one. Their opposed natures can be tracked from brain structure and function to neurodevelopmental paths, to cognitive abilities (Crespi and Badcock, 2008). We have previously shown as well that SZ and ASD patients process language differently, and exhibit distinctive, disorder-specific oscillatory profiles when computing language (Murphy and Benítez-Burraco, 2016b). Similarly to SZ, language deficits in ASD can be linked to many of the changes occurred during our speciation, to the extent that candidates for this condition are also overrepresented among the genes believed to account for the evolution of our language-readiness (see Benítez-Burraco and Murphy, 2016).

In this paper we wish to explore the possibility that SZ patients exhibit exacerbated, disease-specific signatures of the "domestication syndrome". If we are right, our hypothesis could pave the way towards exploring the etiopathogenesis of SZ, and related language impairment, under an original standpoint. To this aim, we begin providing a general account of the domesticated traits found in SZ patients. Thereafter, we will focus on the molecular etiopathogenesis of SZ and check whether genes that have been found involved in the domestication process are somehow represented among SZ candidates. Considering the relevant role of the neural NC in

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

the domestication process, we also consider, in this search, genes involved in NC development and function. Through this comparative evaluation of candidates, we will define a subset of overlapping genes involved in both SZ and in domestication and/or NC. The functional role of these selected genes will be discussed in detail, focusing on their contribution to etiopathogenesis of SZ and their implication for cognition and language. In addition, in order to evaluate their actual functional involvement, we will delve into their differential expression profiles in the SZ brain, by *in silico* analysis of previously published data.

Environmental factors are known to contribute to SZ too (see Brown, 2011; Geoffroy et al., 2013; Moran et al., 2016, for reviews). Likewise, although domestication has genetic roots (as originally suggested by Wilkins et al. and as we will show here), domestication results as well in the creation of a cultural niche that favours the maintenance of domestic features by cultural evolution. Accordingly, although our focus is put on the genes, the role of the environment cannot be dismissed. The same is true for language indeed, as suggested above. Modern language seemingly evolved as the result of changes in brain genes that brought about a differential cognitive ability (aka *language-readiness*) and favoured a domesticated phenotype in our species, but it is also a consequence of subsequent changes in the (proto)linguistic systems, that were triggered and facilitated by the domestic environment in which human beings are reared.

2. Domestication features in SZ

Most of the features observed in the "domestication syndrome" described by Wilkins and colleagues (2014) are found generally exacerbated in SZ individuals (Figure 1). Domestic varieties of mammals exhibit a distinctive set of common traits (Figure 1, top), including neoteny, shorter reproductive cycles, depigmentation, and increased tameness. Changes in behaviour seemingly result from reduced levels of stress hormones (including adrenocorticoids, adrenocorticotropic hormone, cortisol, and corticosterone), and particularly, from the delay in the maturation of the adrenal glands, which also gives rise to an increase of the duration of the immaturity of the hypothalamic-pituitary-adrenal system (the HPA axis) and a hypofunction of the sympathetic nervous system, which provides the animal with a longer socialization window. Many of the differences with their wild conspecifics concern to the craniofacial area. These include changes in ear size and shape, changes in the orofacial area (including shorter snouts and smaller jaws), changes in dentition (particularly, smaller teeth), and a reduced brain capacity (specifically, of components of the forebrain such as the amygdala or parts of the limbic system) (see Wilkins et al., 2014 and Sánchez-Villagra et al., 2016 for details). Below we provide with a detailed description of domestication traits commonly found in schizophrenic patients (Figure 1, down).

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

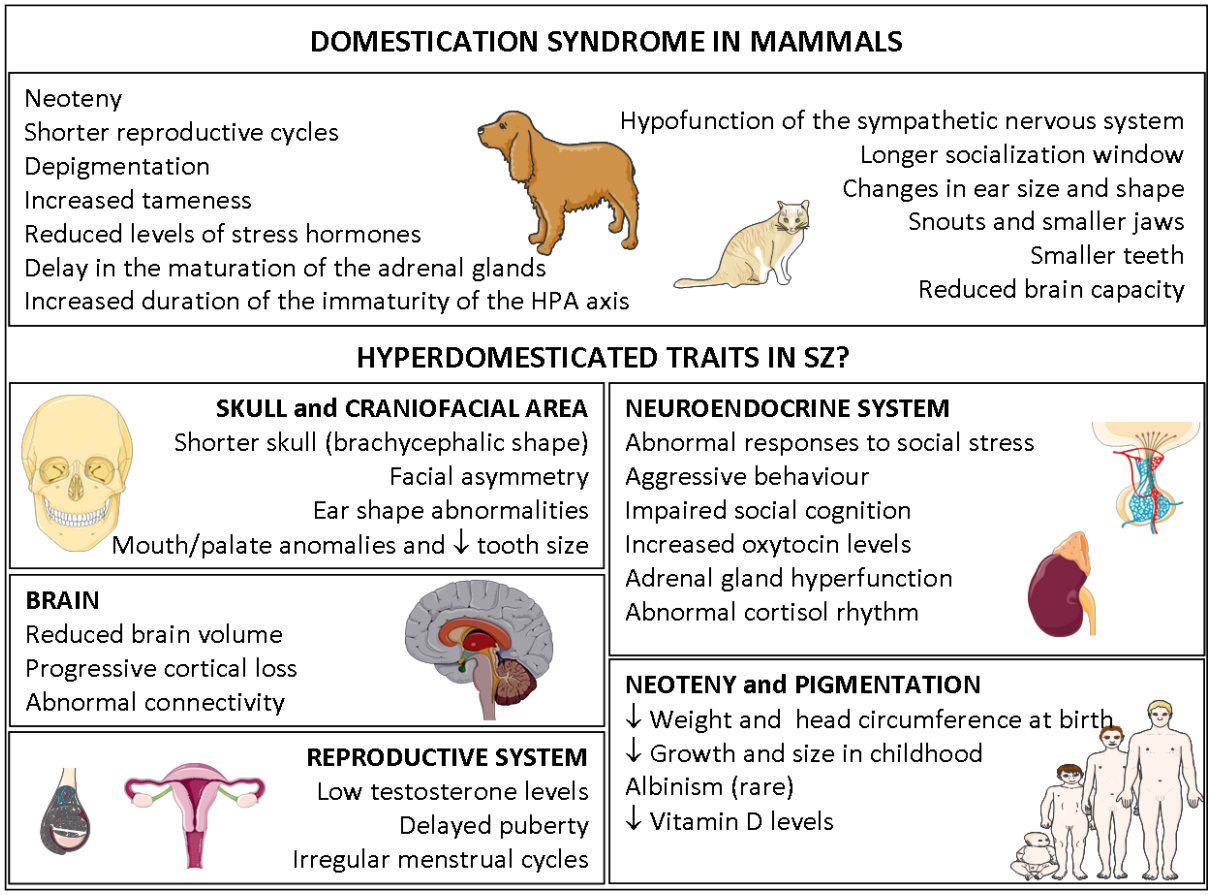


Figure 1. Schizophrenia and the domestication syndrome. The diagram is meant to symbolize the anomalous presentation of the "domestication syndrome" in people with schizophrenia. Main features observed in domesticated mammals (Wilkins et al., 2014, Sánchez-Villlagra, 2016) are shown in the upper box, while selected clinical findings from the SZ spectrum, that may resemble «hyper-domesticated traits», are categorized below. Pictures were gathered and modified from "Slide kit Servier Medical Art" (available at www.servier.com).

Physical anomalies

Minor dysmorphisms are typically featured in the craniofacial area of SZ patients. Indeed, facial asymmetries, particularly those arising along the midfacial junctions (between frontonasal and maxillary prominence derivatives), are reproducibly found in these patients (Gourion et al., 2004, Deutsch et al., 2015). Additionally, ear shape abnormalities (including adherent ear lobes, lower edges of the ears extending backward/upward, malformed ears, asymmetrical ears, or cuspidal ears) are usually observed in SZ phenotypes (Yoshitsugu et al., 2006, Akabaliev et al., 2011, Lin et al., 2012). Some of these features (like prominent crux of helix and ear lobe crease, or primitive shape of the ear) are considered as pathognomonic for SZ in the differential diagnosis of psychotic conditions (Trixler et al., 2001, Praharaj et al., 2012). Anomalies in the mouth (e.g. decreased tooth size, abnormal palate shape and size) are also commonly observed in schizophrenics (Ismail et al., 1998, Rajchgot et al., 2009, Hajnal et al., 2016). Likewise, the odds of having a psychotic disorder seem to be increased in people with shorter and wider palates (McGrath et al., 2002). More generally, the odds of having a psychotic disorder seem to be increased in people with smaller lower-facial heights (glabella to subnasal) (McGrath et al., 2002). Some studies suggest a significant association between minor physical anomalies and the early onset of the disease (Hata et al., 2003).

Brain anomalies and dysfunctions

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Metanalyses of structural neuroimaging studies in the SZ brain are indicative of a significant reduction of total brain volume, which mostly affects to the hippocampus, the thalamus and the cortex, most pronounced in the frontal and temporal lobes (Steen et al., 2006, Haijma et al., 2013, Haukvik et al., 2013). This is seemingly due to the impairment of the surface expansion of the cortex during brain growth, which impacts more on the left hemisphere and results in a relative areal contraction of diverse functional networks (Palaniyappan et al., 2011). Gray matter reduction in SZ is also associated with longer duration of illness and reduced sensitivity to antipsychotic medications. Accordingly, brain volume constraints in SZ are better explained as a combination of early neurodevelopmental disturbance and disease progression (Haijma et al., 2013). Metanalyses of longitudinal neuroimaging studies of the schizophrenic brain further suggest that SZ entails a disorder-specific trajectory of morphological change (compared to other similar conditions like bipolar disorder), which is characterised by a progressive grey matter loss confined to fronto-temporal cortical regions (De Peri et al., 2012, Liberg et al., 2016). Children with childhood onset SZ revels that SZ is characterised by reduced cerebral volume and cortical thickness during childhood and adolescence, which is levelled off in adulthood, as well as by deficits in local connectivity and increased long-range connectivity (Baribeau and Anagnostou, 2013).

The reduction of brain volume is expected to impact cognitive and language abilities of patients and to account for distinctive symptoms of the disease (see also section 5). Specifically, schizophrenic patients with FTD show clusters of volume reduction in the medial frontal and orbitofrontal cortex bilaterally (related to poverty of content of speech), and in two left-sided areas approximating to Broca's and Wernicke's areas (related to the fluent disorganization component of FTD) (Sans-Sansa et al., 2013). Likewise, reduced brain activity in the left pars triangularis of Broca’s area positively correlates with volume reduction of this area (Iwashiro et al., 2016). Interestingly, antipsychotic-naive patients show more pronounced volume reductions in caudate nucleus and thalamus (Haijma et al., 2013), which play a key role in language processing (Murphy, 2015). Finally, we wish highlight that amygdala volume is usually reduced in schizophrenics (Li et al., 2015, Okada et al., 2016, Rich et al., 2016).

Behavioural traits and neuroendocrine impairment

Aggressive behaviour, being involved in the behavioural traits of the “domestication syndrome”, is frequent in SZ, and paranoid belief may associate with it (Darrell-Berry et al., 2016). Interestingly, no positive correlation seems to exist between physical aggression and neuropsychological performance in patients (unless they have attained severe impairment that induces constant uncontrollable outbursts) (Lapierre et al., 1995).

SZ involves as well an impairment of social cognition. Oxytocin is a neuropeptide hormone that, within a wide range of organic functions, is able to affect social interactions and response to social stimuli at various levels (reviewed by Romano et al., 2016). Specifically, it has been recently argued to modulate the multimodality that characterizes our higher-order linguistic abilities (Theofanopoulou, 2016). Oxytocin promotes social play in domestic dogs and the appropriate use of human social cues (Oliva et al., 2015, Romero et al., 2015). A positive correlation between the SZ progression and oxytocin levels in the central nervous system has been observed (Beckmann et al., 1985), which is plausibly explained by a decreased sensitivity to the hormone (Strauss et al., 2015, Glovinsky et al., 1994, Sasayama et al., 2012). Treatment with oxytocin indeed improves verbal memory learning tasks in SZ patients (Feifel et al., 2012), and attenuates the negative symptoms of the disease (Feifel et al., 2010, Modabbernia et al., 2013, Gibson et al., 2014, Davis et al., 2014).

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

The hypothalamus-pituitary axis (HPA) is also affected in SZ, with both hyper- and hypo-function being described (Bradley and Dinan, 2010). Accordingly, heightened cortisol levels are observed in patients with SZ, especially in those who are not medicated (Walker et al., 2008). At the same time, Hempel et al., (2010) found that cortisol concentration in the plasma decreases more markedly during the day in SZ patients than in healthy controls, and that the decrease of HPA axis sensitivity correlates with the severity of negative symptoms. In male patients, diagnosed with first-episode SZ, higher afternoon cortisol levels at the beginning of medical treatment are related to impaired memory performance (Havelka et al., 2016). Girshkin et al., (2016) found that SZ patients do not show significant differences in waking cortisol levels, in the cortisol awakening response, or in immediate post-cortisol awakening control decline compared to controls. However, they also found that they exhibit a significant absence of the increase in cortisol responsivity to stress. According to Ciufolini et al., (2014), SZ is characterised by an attenuated HPA axis response to social stress: despite a normal cortisol production rate, schizophrenics have lower cortisol levels than controls, both in anticipation and after exposure to social stress. In the TD population, HPA activity increases around puberty, with a postpubertal rise in baseline cortisol secretion linked with pubertal stage (Walker et al., 2001, Gunnar et al., 2009). It has been suggested that delayed adrenarche correlates with a higher risk for SZ (Saugstad 1989a, 1989b).

Other features

With regard to neoteny, it is noteworthy that SZ patients exhibit lower weight and reduced head circumference at birth (Cannon et al., 2002), along with slower growth rates and smaller sizes in childhood (Gunnell et al., 2003, Haukka et al., 2008).

Reproductive cycles are also affected in both male and female SZ patients. Delayed age at puberty is associated with greater severity of negative SZ prodromal symptoms in males (Ramanathan et al., 2015). In women higher negative symptom scores and greater functional impairment correlate with later age of menarche (Hochman and Levine 2004). Nearly 50% of women with SZ have irregular menses that are frequently associated to low levels of oestradiol, although no differences in their neuropsychological status have been found compared to patients with regular menses (Gleeson et al., 2016). There is ample evidence of the protective effect of estradiol with respect to SZ, because it interacts with the neurotransmitter systems implicated in the disease, and because it enhances cognition and memory, and reverses the symptoms (Gogos et al., 2015). Men with SZ have, indeed, lower levels of testosterone than healthy controls, and an inverse correlation between serum testosterone and negative symptoms of the disease has been described (Ramsey et al., 2013, Sisek-Šprem et al., 2015). However, in more aggressive patients this correlation is not found (Sisek-Šprem et al., 2015). Interestingly, circulating testosterone levels in schizophrenic males predict performance on verbal memory, processing speed, and working memory (Moore et al., 2013). Men with SZ show a less pronounced activation of the middle frontal gyrus when inhibiting response to negative stimuli, and this response is inversely related to testosterone level, contrary to what is observed in healthy subjects (Vercammen et al., 2013). Testosterone significantly affects brain development, particularly targeting the hypothalamus, the amygdala, and the hippocampus, and impacting on aspects of memory consolidation (Filová et al., 2013).

Lastly, concerning changes in pigmentation, an association between SZ and albinism has been occasionally reported (Clarke and Buckley, 1989). In turn, hyperpigmentation is typically described as a side effect of neuroleptic drugs (specifically, of phenothiazines) used in SZ treatment (Otreba et al., 2015). Interestingly, low serum vitamin D levels have been found in SZ patients and they correlate with the severity of psychotic symptoms (Yüksel et al., 2014).

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

The molecular background for this link may rely on shared features of latitude-adaptation observed in both SZ- and vitamin D-related genes, which suggest that SZ etiopathogenesis may encounter latitude dependent adaptive changes in vitamin D metabolism (Amato et al., 2010).

As noted in section 1, the constellation of symptoms that characterize the "domestication syndrome" have been hypothesised to result as the unselected by-product of a reduce input in NC cells (Wilkins et al., 2014). The phenotypical presentation of human neurocristopathies commonly includes features that have been described in domesticated mammals (Sánchez-Villagra et al., 2016). Interestingly, well-defined neurocristopathies like velocardiofacial syndrome (OMIM#192430) and Di George syndrome (OMIM#188400), involve schizophrenic features (Mølsted et al., 2010, Zhang et al., 2014, Escot et al., 2016). Likewise, given the NC derivation of most craniofacial structures, craniofacial abnormalities observed in SZ are believed to result from disturbances in the neuroectoderm development, hence representing putative external biomarkers of atypical brain growth (Comptom et al., 2007, Aksoy-Poyraz et al., 2011), and suggesting an additional connection between SZ and domestication, at the level of NC functional implication.

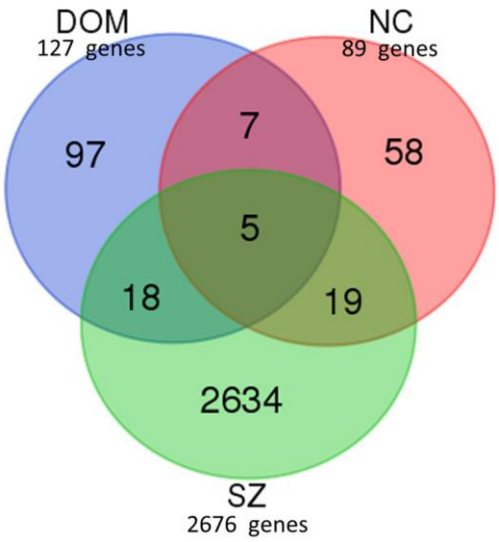
3. Genetic signature of domestication/neural crest features in the SZ molecular background.

In order to delve into the molecular background of our hypothesis, we first assessed whether genes that are involved in SZ etiopathogenesis are represented among candidates for domestication and NC development and function. To this aim, we gathered an extended an up-to-date list of SZ-associated genes, through literature mining and database search (using the Schizophrenia Database, http://www.szdb.org/). The list includes 2689 genes with different levels of evidence: genes bearing pathogenic SNPs, genes found mutated in familial forms of the disease, genes resulting from candidate gene approaches and functional studies, genes resulting from GWA and CNV/exome sequencing studies, and genes showing alternative methylation patterns (see the entire list and corresponding details in Supplemental file 1). Regarding candidates for domestication, we have implemented an enlarged list of candidates, which includes the core set of genes proposed by Wilkins and colleagues (2014), along with additional candidates derived from genetic studies performed in different species. The entire list of domestication candidates comprises 127 genes, detailed in Supplemental file 2. Finally, the third gene list considered in the analysis includes genes related to NC development and function. This list comprises 89 genes (see Supplemental file 3) gathered using functional and pathogenic criteria: NC markers, neurochristopathy-associated genes annotated in the OMIM database, genes that are functionally involved in NC induction and specification, genes involved in NC signalling (within NC-derived structures), and genes involved in cranial NC differentiation.

To search the intersections among the three different sets of genes we have employed a simple Venn diagram (Figure 2), drawn using the software designed and made available as a webtool, by the bioinformatics evolutionary genomics group, at the University of Gent (Belgium; webpage: bioinformatics.psb.ugent.be/webtools/Venn/). A Venn diagram shows all possible logical relations between a finite collection of different sets; the diagram consists of multiple overlapping circles, each representing a set.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Gene Symbol	Entrez ID	SZ	DOM	NC
ABCG1	9619	+	+	
BDNF	627	+		+
BMPR1B	658	+	+	
CACNA1D	776	+	+	
CDH2	1000	+		+
COX4I1	1327	+	+	
CRKL	1399	+		+
DLGAP1	9229	+	+	
DLX5	1749	+		+
DLX6	1750	+		+
EVC2	132884	+	+	
FOXD3	27022	+	+	+
GDNF	2668	+	+	+
GFAP	2670	+		+
GLI3	2737	+		+
GRID1	2894	+	+	
HES1	3280	+		+
IMMP2L	83943	+	+	
JPH3	57338	+	+	
KDM6B	23135	+	+	
KIF1B	23095	+		+



Gene Symbol	Entrez ID	SZ	DOM	NC
MSX1	4487	+		+
NEUROG1	4762	+		+
NF1	4763	+		+
NIPBL	25836	+	+	
NTM	50863	+	+	
OLIG2	10215	+		+
POMT1	10585	+		+
RET	5979	+	+	+
RHOB	388	+		+
ROBO1	6091	+		+
ROBO2	6092	+		+
SKI	6497	+	+	
SOX10	6663	+	+	+
SOX9	6662	+	+	+
SYNJ2	8871	+	+	
TBX1	6899	+		+
TPH1	7166	+	+	
TRPM1	4308	+	+	
VDAC1	7416	+	+	
WNK2	65268	+	+	
ZEB2	9839	+		+

Figure 2. Genetic overlap among schizophrenia, domestication, and neural crest signatures. Venn diagrams show the intersection among the extended list of genes considered as either genomic or functional candidates for schizophrenia (SZ, see Supplemental file 1), domestication (DOM, see Supplemental file 2) and neural crest (NC, see Supplemental file 3). See text for details.

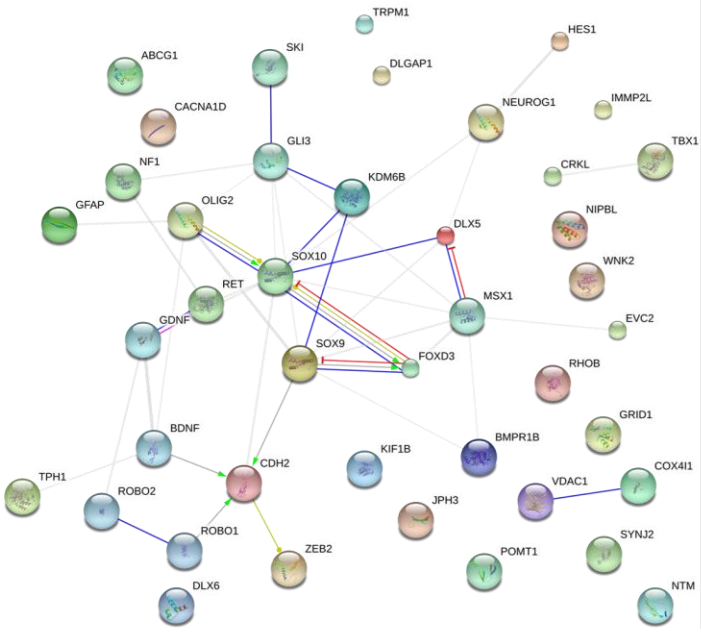
As shown in Figure 2, an overall number of 42 genes were found among the intersection sets of the diagram. In particular, 5 genes (*FOXD3*, *RET*, *SOX9*, *SOX10* and *GDNF*) were overlapping within the three gene lists, hence could represent a selected core of candidates that support our hypothesis. In addition, 18 genes were shared between the SZ list and the domestication list, while 19 genes were shared between SZ and NC candidates. Overall, we found out that over 18% (23 out of 127) of domestication candidates, and 27% (24 out of 89) of genes involved in NC development and function, are listed within those that have been documented as playing a role, as either putative candidates for, or functionally related to SZ. Considering domestication (n: 127) and neural crest (n: 89) candidates altogether, this list comprises 19.4% (42 of 216) SZ candidates.

Below we provide with a brief functional characterization and biological interpretation of these genes.

4. Functional implication and biological interpretation of domestication/NC genes in the SZ brain.

We expected that the 42 genes we highlight here as part of the shared signature of domestication and/or NC and SZ (see Figure 2) are functionally interconnected and map on to specific signaling cascades, regulatory pathways, or aspects of brain development and function, of interest for SZ etiopathogenesis, and specifically, for language deficits in this condition. Accordingly, we have employed the license free software for gene network analysis String 10 (www.string-db.org). This allowed predicting quite robust links among the genes. In particular, the core genes (*FOXD3*, *GDNF*, *RET*, *SOX9*, and *SOX10*) are all reciprocally interconnected, hence displayed in the central part of the network (Figure 3). These genes are indeed involved in different steps of NC development and neural specification.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.



BIOLOGICAL PROCESS			
Pathway ID	*Pathway description*	*# Genes*	*FDR*
GO.0045597	positive regulation of cell differentiation	16	7.91e-09
GO.0048468	cell development	20	9.1e-09
GO.0007399	nervous system development	21	1.42e-08
GO.0007423	sensory organ development	13	1.42e-08
GO.0010001	glial cell differentiation	9	1.42e-08
GO.0051094	positive regulation of developmental process	17	1.42e-08
GO.0030182	neuron differentiation	16	1.96e-08
GO.0048864	stem cell development	10	4.71e-08
GO.0042063	gliogenesis	9	4.89e-08
GO.0045595	regulation of cell differentiation	18	4.89e-08
MOLECULAR FUNCTION			
Pathway ID	*Pathway description*	*# Genes*	*FDR*
GO.0043565	sequence-specific DNA binding	10	0.0164
GO.0000981	RNA polymerase II transcription factor activity sequence-specific DNA binding	8	0.0175
GO.0003700	transcription factor activity, sequence-specific DNA binding	10	0.0175
GO.0044212	transcription regulatory region DNA binding	8	0.0175
GO.0003682	chromatin binding	7	0.0198
CELLULAR COMPONENT			
pathway ID	*pathway description*	*# Genes*	*FDR*
GO.0042995	cell projection	14	0.000995
GO.0097458	neuron part	12	0.000995
GO.0043005	neuron projection	10	0.0021

Figure 3. Gene interaction network. The diagram shows the network of known and predicted interactions among genes proposed as candidates for SZ and domestication and/or NC development and function (genes with positive tags in the last two right-sided columns in Figure 2). The network was drawn with String (version 10.0; Szklarczyk et al., 2015)) license-free software (http://string-db.org/), using the molecular action visualization. Colored nodes symbolize gene/proteins included in the query (small nodes are for proteins with unknown 3D structure, while large nodes are for those with known structures). The color of the edges represent different kind of known protein-protein associations. Green: activation, red: inhibition, dark blue: binding, light blue: phenotype, dark purple: catalysis, light purple: post-translational modification, black: reaction, yellow: transcriptional regulation. Edges ending in an arrow symbolize positive effects, edges ending in a bar symbolize negative effects, whereas edges ending in a circle symbolize unspecified effects. Grey edges symbolize predicted links based on literature search (co-mentioned in PubMed abstracts). Stronger associations between proteins are represented by thicker lines. The medium confidence value was .0400 (a 40% probability that a predicted link exists between two enzymes in the same metabolic map in the KEGG database: http://www.genome.jp/kegg/pathway.html). The diagram only represents the potential connectivity between the involved proteins, which has to be mapped onto particular biochemical networks, signaling pathways, cellular properties, aspects of neuronal function, or cell-types of interest. Functional enrichment of the entire gene set, according to Gene Ontology (GO) consortium annotations, was performed using String algorithm for gene network analysis; the output is provided in the table on the right. FDR: false-discovery rate, obtained after Bonferroni correction. A FDR cutoff of 0.05 was set to select significant functions. For the "biological process" and "molecular function" annotations, only the top ten scoring categories are displayed.

RET gene is a core domestication candidate (Wilkins et al., 2014), which encodes a tyrosine-protein kinase involved in NC development, and is found deleted in SZ patients (Glessner et al., 2010). *SOX* genes encode master transcriptional regulators of cell-fate programming during development. In particular, *SOX9* and *SOX10* are members of the soxE group, involved in NC development and differentiation (Cheung and Briscoe, 2003). *SOX9* acts specifically in craniofacial development, downstream of WNT and BMP pathways (Liu et al., 2013b), and has been found reproducibly upregulated in SZ brains (Shao and Vawter, 2008, Chen et al., 2013, Lanz et al., 2014). *SOX10* regulates NC stem cells balance during development; it is functionally related to the SZ-susceptibility gene *DISC1* during early NC cell migration (Drerup et al., 2009), and oligodendrocyte differentiation (Hattori et al., 2014). *SOX10* is found hypermethylated in the brain of SZ patients (Iwamoto et al., 2005) and carries SNPs that have

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

been related to the age of onset of clinical manifestations (Yuan et al., 2013). *RET* and *SOX10* are co-expressed as reliable markers in enteric nervous system, although their functional interaction is not clear (Hetz et al., 2014). In turn, *FOXD3* is required during NC development and regulates dorsal mesoderm development in the zebrafish (Chang and Kessler, 2010). The gene locus maps within one of the AMH-specific differentially-methylated genomic regions (Gokhman et al., 2014), suggesting that changes in the gene functional status may have occurred during recent human evolution. *FOXD3* is also a transcriptional target of the SZ-candidate *DISC1*, and is involved in cranial NC migration and differentiation (Drerup et al., 2009). *SOX9* and *SOX10* indirectly interact through *FOXD3*, as shown in Figure 3, being coexpressed at different stages of NC development. In particular, *SOX9* seems to drive the expression of both *SOX10* and *FOXD3* (Cheung and Briscoe, 2003). Finally, *GDNF* is also a core candidate for the domesticated phenotype in mammals (Wilkins et al., 2014). It encodes a neurospecific factor involved in the differentiation of dopaminergic neurons and in synaptogenesis (Christophersen et al., 2007, Ledda et al., 2007). GDNF levels are lower in SZ patients compared with healthy controls (Tunca et al., 2015). With regard to gene networking, GDNF contributes to the activation of RET protein-tyrosine kinase (Jing et al., 1996), mediating neuronal survival (Coulpier et al., 2002).

Other genes in the network are directly or indirectly related to the core genes described above. In particular, *MSX1* and *DLX5* homeotic genes also appear to play pivotal roles in this gene network, as they establish functional interactions with many of the candidates shown in Figure 3. Interestingly, *MSX* genes control the spatial organization of the NC-derived craniofacial skeleton (Attanasio et al., 2013, Khadka et al., 2006, Han et al., 2007, Gitton et al., 2011). Also *DLX* homeobox genes function in early NC development, and also in late specification of NC-derived structures (McLarren et al., 2003, Ruest et al., 2003), and play key roles as well in skull and brain development (Jones and Rubinstein, 2004, Kraus and Lufkin, 2006, Vincentz et al., 2016). In particular, *MSX1* encodes a transcriptional repressor specifically involved in odontogenesis (Alappat et al., 2003, Cohen, 2000), hence mutated in orofacial clefting and tooth agenesis (Liang et al., 2016). *MSX1* is a direct downstream target of *DLX5* during early inner ear development (Sajan et al., 2011). Methylation changes in *MSX1* are found in the hippocampus of SZ patients, as a part of the circuit-specific DNA methylation changes affecting the glutamate decarboxylase 1 regulatory network in SZ, which may explain GABAergic dysfunctions in this condition (Ruzicka et al., 2015).

Among the other shared candidates between SZ and domestication, *KDM6B* and *BMPR1B* are shown to interact with *SOX9* and *SOX10* (see Figure 3). *KDM6B* encodes a histone demethylase, which plays a central role in regulation of posterior development. In particular, it activates neuronal gene expression during postnatal and adult brain neurogenesis in the subventricular zone (Park et al., 2014). A frameshift mutation, with unknown functional consequences, has been found in this gene, through whole exome sequencing (WES) of SZ family trios (Fromer et al., 2014). In turn, *BMPR1B* encodes a receptor for bone morphogenetic proteins (BMPs), that are pleiotropic morphogens acting in both bone and neural development. The interaction with *SOX9* is well characterized during postnatal chondrogenesis (Jing et al., 2014). Type Ib BMP receptors also mediate the rate of commissural axon extension in the developing spinal cord (Yamauchi et al., 2013), and, in mice, are involved in supraxial nervous functions (Caronia et al., 2010). *BMPRIB* is annotated among the putative SZ epigenetic signature genes, resulting from genome-wide methylome studies (Aberg et al., 2014).

Also *GLI3* is widely functionally involved in this network. This gene encodes a key mediator of the hedgehog signalling in vertebrates, acting as a repressor in dorsal brain regions (Haddad-

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Tóvolli et al., 2012). It controls cortical size by regulating the primary cilium-dependent neuronal migration (Wilson et al., 2012). With regards to SZ, a *de novo* missense mutation in *GLI3* has been recently identified through WES (Fromer et al., 2014). *GLI3* has been found to interact, both *in vivo* and *in vitro*, with *SKI* (Ravasi et al., 2010). This gene encodes a transcription factor that regulates TGFβ signaling and is mutated in nearly 90% of cases of Shprintzen-Goldberg syndrome (OMIM#182212), a condition entailing craniofacial and brain anomalies (Au et al., 2014). This gene is found methylated in SZ patients (Montano et al., 2016). Indeed, in the brain, *SKI* regulates the proliferation and differentiation of neural precursors, along with the specification of cortical projections (Lyons et al., 1994, Baranek and Atanasoski 2012). In the mouse embryo, *Ski* is expressed in the migrating NCCs and in NC derivatives (Lyons et al., 1994).

OLIG2 encodes a transcription factor that interacts with SOX proteins, and plays a key role in the regulation of ventral neuroectodermal progenitor cell fate. Specifically, it is essential for oligodendrocyte function, whose impairment is thought to be a primary pathogenic event in SZ, specifically affecting the prefrontal cortex (Georgieva et al., 2006, Mauney et al., 2015). Indeed, in our network *OLIG2* is also linked to *GFAP*, which encodes a hallmark structural component of mature astrocytes. Interestingly, *GFAP* levels are upregulated in the left posterior superior temporal gyrus (Wernicke's area) of schizophrenics (Martins de Souza et al., 2009).

Another key node in the network is represented by the *CDH2* gene, which encodes a member of the cadherin superfamily involved in the formation of cartilage and bone, the establishment of left-right asymmetry, and the development of the nervous system (Kadowaki et al., 2007, Martínez-Garay et al., 2016)). Inactivation of *CDH2* in the dorsal telencephalon results in a "double cortex" phenotype, with heterotopic gray matter interposed between zones of white matter (Gil-Sanz et al., 2014). *CDH2* indeed regulates the proliferation and differentiation of ventral midbrain dopaminergic progenitors, the organization of excitatory and inhibitory synaptic circuits, and long-term potentiation in the adult hippocampus (Bozdagi et al., 2010, Sakane and Miyamoto 2013, Nikitczuk et al., 2014). The gene was found mutated in schizophrenics in a WES study (Purcell et al., 2016). *CDH2* integrates *SOX9* signaling and regulates *OLIG2* in neuroepithelial lineage cells, during vertebrate brain development (Sasai et al., 2014). Also, CDH2 cooperates with the BDNF in the aggregation, assembly and mobilization of synaptic vesicles (Bury and Sabo, 2014). *BDNF* encodes a nerve growth factor needed for neuronal survival and synaptic plasticity. Common variants/polymorphisms of the gene have been associated with specific cognitive processes (see Goldberg and Weinberger 2004, González-Giraldo et al., 2014, Jasińska et al., 2016, Wegman et al., 2016) and with the cognitive performance of people suffering from neuropsychiatric conditions. In particular, abnormally low levels of BDNF have been detected in schizophrenics (Palomino et al., 2006). Functional genomics has indeed identified *BDNF* among a list of reliable SZ candidates, contributing to the genetic background for the neurodevelopmental abnormalities leading to the disrupted connectivity occurring in the disease (Ayalew et al., 2012). Being implicated in axonogenesis and neural cell polarization, *CDH2* is also indirectly related to *ROBO* genes. *ROBO1* and *ROBO2* encode highly conserved transmembrane receptors that function in axon guidance and neuronal precursor cell migration. Mutations in *ROBO* genes have been linked to human neurodevelopmental disorders, as discussed in the next section. Noticeably, functional genomics analyses have identified both *ROBO1* and *ROBO2* as candidate loci for SZ risk (Potkin et al., 2009, 2010). Finally, *ZEB2* appears as an additional functional partner of *CDH2* in the network (Figure 3). This gene encodes a transcriptional factor, which acts as an essential regulator of neuroectoderm and NC development, contributing to the development of the neocortex and the hippocampus (Hegarty et al., 2015). Besides being mutated in the

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Mowat-Wilson syndrome (OMIM#235730), a condition characterized by Hirschsprung disease, craniofacial dismorphisms, and intellectual disability (Adam et al., 2006, Garavelli et al., 2016), *ZEB2* maps within a SZ-associated locus, thus possibly representing a player in the polygenic etiology of this condition (Ripke et al., 2013, Bigdeli et al., 2016).

Other candidate genes are not clearly functionally interconnected in the core interacting network (see Figure 3), although most of them play relevant roles in cognitive functions that have evolved in humans. Most of them are further discussed in section 5 because of their impact on language development.

The functional enrichment, based on gene ontology (GO) annotations, of the gene list considered in this study (Figure 2), point out that most of these genes act in signaling pathways known to be impaired in SZ and might play biological functions that are affected in this condition (see GO annotation table in Figure 3). Noticeably, the top-scoring functional categories, resulting from the functional annotations, include regulation of nervous system development and of cell differentiation, specifically of glial cells and neurons. Among the molecular function GO categories, transcription regulation hits as the most relevant; indeed, many of the genes listed here encode transcription factors and epigenetic modulators, that on their turn modulate the expression of genes with pleiotropic role in brain development, cognitive abilities (including language processing). Finally, considering the cellular localization of the proteins, most of them appear to localize inside the cell projection components, confirming their role as regulators of neuron interconnection.

We have further attempted to delve into the actual functional implication of these selected genes in the SZ molecular pathogenesis, by assessing whether their expression is significantly modulated in the SZ brain. To this aim, we surveyed the Gene Expression Omnibus (GEO) repository (https://www.ncbi.nlm.nih.gov/gds) searching for gene expression datasets obtained from SZ brain profiling. The following dataset were selected and corresponding data were gathered: GSE53987 (prefrontal cortex, hippocampus, and associative striatum; Lanz et al, 2014), GSE4036 (cerebellum; Perrone-Bizzozzero, unpublished data), GSE21935 (temporal cortex; Barnes et al, 2011); GSE35977 (parietal cortex; Chen et al, 2013); GSE62191 (frontal cortex; de Baumont et al, 2015). The specified datasets were selected based on their homogeneous and comparable study design. Additional details are provided in Table 1. Specifically, all datasets were obtained by means of genome-wide microarray expression profiling of dissected cadaveric brain tissues from SZ patients and matched controls. Raw datasets were individually analyzed *in silico* as previously described (Benítez-Burraco et al., 2016). Briefly, the GEO2R tool (http://www.ncbi.nlm.nih.gov/geo/geo2r/; Barrett et al., 2013) was used to compare patients-versus-controls normalized probeset intensities provided by the submitters. The p-value was adjusted, whenever appropriate, using Bonferroni-Hochberg correction for false discovery rate (FDR). A p-value cutoff <0.05 was set for filtering data. Base 2 logarithm transformation of fold changes (logFC) were applied to obtain relative expression changes between SZ patients and corresponding controls.

Table 1. Dataset description

GEO accession	Tissue type (brain region)	Experimental groups/Disease status	*n**	Array Type/Platform	Reference
GSE4036	Cerebellum (crus I/VIIa area)	SZ CONTROL	14 14	Affymetrix Human Genome U133 Plus 2.0 Array	Perrone-Bizzozzero, unpublished

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

GSE21935	Superior temporal cortex (Brodmann Area 22)	SZ CONTROL	23 19	Affymetrix Human Genome U133 Plus 2.0 Array	Barnes et al., 2011
GSE62191	Frontal cortex	SZ CONTROL	29 30	Agilent-014850 Whole Human Genome Microarray 4x44K G4112F	De Baumont et al., 2015
GSE53987	Associative striatum Prefrontal cortex Hiipocampus	SZ CONTROL SZ CONTROL SZ CONTROL	18 18 19 19 15 18	Affymetrix Human Genome U133 Plus 2.0 Array	Lanz et al., 2014
GSE35977	Parietal cortex	SZ CONTROL	4 5	Affymetrix Human Gene 1.0 ST Array [transcript (gene) version]	Chen et al., 2013

* each sample corresponds to a single individual (i.e. biological replicate).

Through this approach, we have obtained cortical area-specific expression profiles of the SZ brain. Complete gene lists of differentially expressed genes obtained from each dataset are provided in Supplemental file 4. Briefly, the cerebellum expression profiles of SZ patients included in the GSE4036 data series yielded over 1800 annotated genes showing statistically significant (p-value<0.05) differential expression over controls. The data analysis of the temporal cortex data included in the GSE21935 dataset yielded nearly 1950 annotated genes (p<0.05). In the frontal cortex (GSE62191 dataset), the expression profile included 727 differentially expressed annotated genes (p<0.05), whereas in the prefrontal cortex, analyzed in an independent study (GSE53987 dataset), it included nearly 6200 genes (p<0.05). Finally, the *in silico* analysis of data included in the GSE53987 dataset allowed also obtaining expression profiles of the associative striatum nucleus (6705 annotated genes, p<0.05) and of the hippocampus (over 4000 genes, p<0.05) of SZ patients.

The extended gene lists of annotated genes obtained from the analysis of each dataset (see supplemental file 4) were then used for searching the selected 42 candidates specified in the previous section. Overall, we found significant differential expression values for over 75% (32 out of 42) of the common candidates for SZ, domestication, and/or NC development and function, as discussed above, namely: *BDNF*, *BMPR1B*, *CACNA1D*, *CDH2*, *COX4I1*, *DLGAP1*, *DLX5*, *DLX6*, *FOXD3*, *GDNF*, *GLI3*, *GRID1*, *HES1*, *IMMP2L*, *JPH3*, *KDM6B*, *KIF1B*, *MSX1*, *NF1*, *NIPBL*, *OLIG2*, *POMT1*, *RET*, *ROBO2*, *SKI*, *SOX9*, *SYNJ2*, *TBX1*, *TPH1*, *VDAC1*, *WNK2* and *ZEB2*. These genes resulted differentially expressed in different brain areas (Figure 4a), the largest number being found within the expression profiles of the frontal cortex (21 genes), the associative striatum nucleus (16 genes), and the hippocampus (11 genes). These functional events are obviously observed in adult (cadaveric) specimens, hence they could not reflect the molecular events that have occurred during early neural development, which are crucial for the etiopathogenesis of SZ. Nonetheless, some insights into the molecular networking that underlie the impaired cognitive and social scenarios acting in the SZ brain could be gathered. Moreover, it is important to note that all these brain areas exhibit anomalies (structural and functional) in schizophrenics, play a role in language processing, and show differences in domesticated animals compared to their wild conspecifics.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

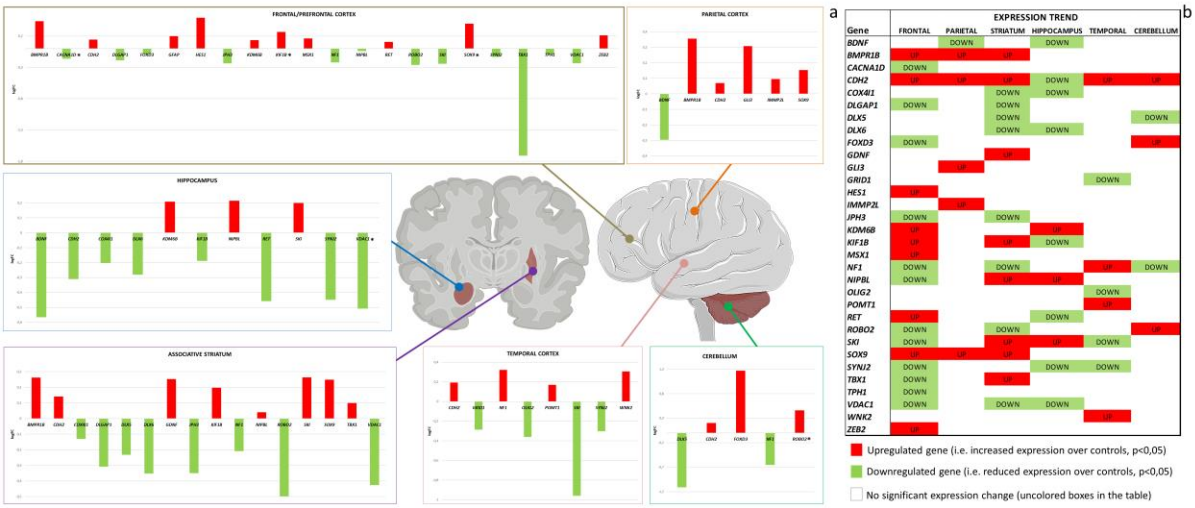


Figure 4. Brain gene expression profiles in SZ patients. The figure on the left (a) illustrates the differential expression of the candidate genes found overlapping between SZ and domestication and/or NC development and function in the tested brain areas. The background diagrams show a coronal section across the midline (on the left) and a lateral view (on the right) of the brain. The pictures were gathered and modified from "Slide kit Servier Medical Art" (available at www.servier.com). In each bar graph: the Y-axis shows the log fold change (logFC) values calculated between SZ patients and controls in each tested dataset (red bar: upregulated gene, green bar: downregulated gene; see text for details). The logFC value of genes labeled with an asterisk was calculated as the mean value of duplicated probeset raw data found in the corresponding dataset (see Supplemental file 4 for extended gene lists). FC values cannot be directly compared when obtained from different datasets (refer to Table 1), as they represent relative expression quantities, normalized over different controls samples in different studies. The expression trends of each gene across the different areas is shown as a cluster view in the image on the right (b).

In the frontal cortex, most of the core-set genes in the gene network displayed in Figure 3 are upregulated, namely *BMPR1B*, *CDH2*, *KDM6B*, *MSX1*, *RET*, *SOX9* and *ZEB2*. A pivotal role in this selected group is played by *SOX9*, whose activation occurs downstream to BMP signaling (Liu et al., 2013b), consistent with the coherent upregulation *BMPR1B*. KDM6B binds and cooperates with SOX9. SOX9 promotes *CDH2* activation (Sasai et al., 2014), which, in turn, induces the SMAD cascade and leads to *ZEB2* transcriptional activation (Bedi et al., 2014). In the same brain area, *FOXD3* (a *SOX9* repressor, based on String10 prediction) is downregulated, along with other 11 candidates (Figure 4a). Interestingly, genes that displayed differentially expression in the frontal cortex of domestic animals (dogs, pigs, rabbits, and guinea pigs) compared to their wild counterparts included a widely conserved *SOX* gene (Albert et al, 2012), strongly supporting the central role of these gene family in the brain changes implicated in the domestication process.

In the temporal cortex, *OLIG2* and *SKI*, among others, show a reduced expression trend (Figure 4a), possibly indicative of the impaired glial function. Indeed, *SKI* methylation was described in SZ brains (Montano et al., 2016).

It is worth noting that structural and functional anomalies in the frontal and temporal cortices of SZ patients are believed to impact greatly on their language abilities. Accordingly, lexical processing in SZ entails abnormal oscillatory patterns in the left frontal-temporal areas, specifically reduced temporal lobe α and left frontal lobe β activity (Xu et al., 2013, Sun et al., 2014). Likewise, complex sentences understanding involves reduced activation in the right posterior temporal and left superior frontal cortex in schizophrenic patients (Kircher et al.,

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

2005). Reduced α and β in left temporal-parietal sites, along with reduced θ at right frontal lobe sites is observed during phrase structure chunking (Ferrarelli et al., 2012, Xu et al., 2012). Interestingly too, the ratio fronto-parietal vs. fronto-temporal connectivity has increased from monkeys to apes to modern humans (Hecht et al., 2013), providing the evolutionary scaffolding for our imitation abilities, which underlie cultural innovation (see Boeckx and Benítez-Burraco 2014a for discussion).

Also in the striatum, key candidates, including *BMPR1B*, *CDH2*, *SOX9*, *GDNF* and *SKI* are coherently upregulated, while *DLX* genes and *ROBO2* are downregulated, suggesting that key molecular markers of NC-derived structures are impaired in this nucleus. The striatum is, indeed, part of the cortical-subcortical loop involved in learning speech sequences for articulation, and in extracting complex regularities in auditory sequences (Krishnan et al., 2016).

With regards to the hippocampus, we have found that eight candidates are downregulated, including *BDNF*, *CDH2*, *DLX6*, and *RET* (Figure 4a). Based on the reciprocal functional connections among these genes, discussed above, their shared expression trends may reflect an altered hippocampal synaptic function. Also *VDAC1* and *COX4I1* are downregulated in this brain region (Figure 4a); these genes are both expressed in the mitochondrion and are involved in energy production and ion homeostasis (Richter et al., 2010, Shoshan-Barmatz et al., 2015). Hence, their downregulation reasonably impacts on brain bioenergetics, in SZ and also in other disorders featuring cognitive impairment (Rosa et al., 2016). Interestingly, *KDM6B*, a target of activin signaling involved in cognitive function and affective behavior (Link et al., 2016), is also upregulated in the SZ hippocampus (Figure 4a). The hippocampal expression of *SKI* gene is increased as well, suggesting aberrant cortical connections in the SZ hippocampus. The hippocampus is involved in language learning (Krishnan et al., 2016), and displays a reduced volume in schizophrenics (Hirayasu et al., 1998), which can be related to phrase chunking difficulties, due to oscillations generated in this region (Murphy, 2015). Interestingly, some domestic animals exhibit changes in the hippocampus that can berelated to differences in their cognitive and behavioral features (Rehkämper et al., 2008).

Finally, few candidates show expression changes in the cerebellum; these include *CDH2*, *FOXD3* and *ROBO2*, coherently upregulated (Figure 4a), confirming their synergic functions, as gathered from the network analysis (see Figure 3). The cerebellum is involved in both motor and non-motor language-related processes, (Mariën et al., 2014, Noroozian 2014), with structural and functional anomalies documented in SZ patients (Keller et al., 2003, Chen et al., 2013)

Taken together, the expression levels of the entire gene set across the tested brain areas suggest that a hallmark of the SZ brain molecular signature is the abnormal activation of the BMP-SOX9-CDH2 axis, given the reproducible upregulation of *BMPR1B*, *CDH2*, *KDM6B*, *SOX9* (in at least two areas; Figure 4b). Conversely, our data show a prevalent repression of *BDNF*, *DLX5-6*, *JPH3 COX4I1*, *DLGAP1*, *NF1*, *SYNJ2* and *VDAC1* in the SZ brain, suggesting the overall impairment of molecular mechanisms affecting neuronal survival, synaptic plasticity and functional, and social cognition (Li et al., 2016, Petrella et al., 2016). We reasonably expect that these changes account in part for the specific cognitive, language, and social phenotype of schizophrenics.

Regarding the biological consequences of this overlapping between domestication and/or NC candidates, and SZ candidates, we wish to add two notes of caution. First, we have found that

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

between 20-30% of candidates for domestication/NC are also related to SZ, whereas roughly 5% of the coding genes of the human genome have been implicated in the disease (according to the Schizophrenia Database). Nonetheless, because of pleiotropy, it may well be that some of these common candidates are not playing the same biological function domestication/NC and in SZ. This possibility has to be confirmed experimentally for each candidate. That said, we have shown that some promising functional overlapping can be found. SZ is a late-developing condition, because important brain changes resulting in the disease (e.g. changes in neural pruning mechanisms) occur during adolescence, whereas domestication mostly results from changes in early developmental stages. Nonetheless, available evidence also suggests that the brain and the cognition of SZ patients develop differentially (compared with typically-developing people) since the very beginning, as shown by studies in presymptomatic patients (Cannon et al., 2015; Liu et al., 2015; Filatova et al., 2017; Sugranyes et al., 2017). At the same time, developmental changes, brought about by the early disturbance of the NC function (and by domestication in general), are expected to have an impact throughout lifespan, particularly, because of its effect on the environment. Accordingly, it is reasonable to claim the existence of a biological overlapping between the etiology of SZ, the role of NC in development, and domestication of the human phenotype.

5. Schizophrenia and (the evolution of) human language

Many of the genes gathered in our selected gene list play a role in the etiopathogenesis of phenotypes affecting the language domain, reinforcing the link between domestication, SZ, and language. In most cases, though, the implication in neural/cognitive functions could be viewed as a side-effect of the wide pleiotropism and extremely heterogeneity of the vast group of genes considered to lay the polygenic foundation of SZ.

DLX genes, including *DLX5* and *DLX6* are also important for the evolution of language-readiness, based on their interaction with *FOXP2* and *RUNX2* (Boeckx and Benítez-Burraco, 2014a). Dlx5/6(+/-) mice show reduced cognitive flexibility that seemingly results from an abnormal pattern of γ rhythms, caused by abnormalities in GABAergic interneurons: this phenotype recapitulates some clinical findings of SZ patients (Cho et al., 2015). During language processing γ rhythms are hypothesised to generate syntactic objects before β holds them in memory and they also contributes to lexical processing (see Murphy 2015 for details). As noted in the previous section, in schizophrenics reduced γ activity is observed at frontal sites during semantic tasks; likewise, higher cross-frequency coupling with occipital α is usually detected (Murphy and Benítez-Burraco, 2016a).

Also *ROBO* genes are core candidates for language evolution (Boeckx and Benítez-Burraco 2014b). *ROBO1* is a candidate for dyslexia and speech-sound disorders (Hannula-Jouppi et al., 2005, Mascheretti et al., 2014), and is involved in the neural establishment of vocal learning abilities (Wang et al., 2015). The *ROBO2* locus is also in linkage with dyslexia and speech-sound disorder and reading (Fisher et al., 2002, Stein et al., 2004), and is associated with expressive vocabulary growth in the unaffected population (St Pourcain et al., 2014).

GLI3 is involved in a craniofacial syndrome involving cognitive impairment, both in humans (Greig cephalopolisyndactily, OMIM#175700) and in mice (Veistinen et al., 2012; Lattanzi et al, in press; Tabler et al., 2016) with cognitive impairment, which entails language delay (McDonald-McGinn et al., 2010, Lattanzi, 2016). Indeed, it regulates skull development acting on the DLX5/RUNX2 cascade (Tanimoto et al., 2012), hence it is expected to have played a role in the physiological events leading to globularization, in which these genes were seemingly

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

involved (Boeckx and Benítez-Burraco, 2014a; Nearly 98% of Altaic Neanderthals and Denisovans gained a non-synonymous change in GLI3 that is described as mildly disruptive (Castellano et al., 2014).

OLIG2 confers susceptibility to SZ, alone and as part of a network of genes implicated in oligodendrocyte function (Georgieva et al., 2006). *OLIG2* is also associated with psychotic symptoms in Alzheimer's disease (Sims et al., 2009) and is up-regulated in the cerebellum of ASD patients (Zeidán-Chuliá et al., 2016).

SKI is mutated in Shprintzen-Goldberg syndrome that features skeletal abnormalities and intellectual disability, including speech and language impairment (Au et al., 2014). Speech impairment has been hypothesized to result from poorer phonological abilities, although changes in the quality of the voice (pitch, nasalization) are also observed in patients (Van Lierde et al., 2007).

A well-known polymorphism of *BDNF* (Val66Met) seemingly influence in the pattern of brain activation and task performance during reading, including reading comprehension and phonological memory (Jasińska et al., 2016). This and other *BDNF* polymorphisms have a proven to impact on the language performance of SZ patients (Kebir et al., 2009, Zhang et al., 2016). BDNF is also mentioned as one of the genes defining the genetic architecture of human developmental language impairment (Li and Bartlett 2012).

In Mowat-Wilson syndrome, due to *ZEB2* mutations, severe impairment of productive language is described (Adam et al., 2006, Garavelli et al., 2016).

NF1 is mutated in neurofibromatosis type 1 (OMIM#162200), a neurogenetic disorder comprising an increased risk for learning and intellectual disabilities, among other major symptoms (Anderson and Gutmann 2015). Affected children may exhibit high rates of social impairment that impact social interaction and skills (Allen et al., 2016; Brei et al., 2014). These might result, in part, from a generalized deficit in the "Theory of Mind" (crucial for language acquisition), which seems to be independent of their general cognitive abilities (Payne et al., 2016). They also feature poor expressive language and preliteracy skills (Lorenzo et al., 2013, 2015). Deficit in fine motor skills usually co-occur, dut to the impairment of fronto-striatal-cerebellar loop (Iannuzzi et al., 2016). Interestingly, heterozygous *Nf1* (+/-) mice show larger brain volumes in the prefrontal cortex, in the caudate and the putamen (part of the language structural network), and in regions involved in social recognition and spatial learning (Petrella et al., 2016). Although these children frequently exhibit ASD symptoms, they outscore IQ-matched children with ASD in eye contact, behavior, and language skills (Garg et al., 2015).

Other genes, not clearly interconnected in the network (see Figure 3), are also clearly implicated in neural functions that are relevant to the language domain.

NIPBL is a candidate for Cornelia de Lange syndrome (OMIM#122470), in which the intellectual disability greatly impacts on the expressive language abilities (Boyle et al., 2015, Parisi et al., 2015). The gene is also a putative candidate for childhood apraxia of speech (Peter et al., 2016).

VDAC1 may reasonably represent a marker of neuronal vulnerability and cognitive impairment, in neurodegenerative conditions including Alzheimer disease (Rosa et al., 2016), and neuronal ceroid lipofuscinoses (Kielar et al 2009). These conditions are characterized by

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

speech and language problems, with a decline in verbal abilities over time (Lamminranta et al., 2001, von Tetzchner et al., 2013).

The region containing *GRID1* has been associated with the parieto-occipital 10-Hz rhythmic activity (Salmela et al., 2016). This α rhythm, which synchronizes distant cortical regions, is involved in lexical decision making and contributes as well to the embedding of γ rhythms generated cross-cortically in order to yield inter-modular set-formation during language processing (see Murphy 2015 for details). This rhythmic activity is found altered in SZ during lexical and sentence processing (Murphy and Benítez-Burraco 2016a).

IMMP2L is a candidate for behavioural disorders, including Gilles de la Tourette syndrome (OMIM#137580) (Bertelsen et al., 2014, Gimelli et al., 2014). In this condition multiple motor and vocal tics are described that impact on language processing (Frank 1978).

Abnormal expansion of repeats in the 3' UTR of *JPH3* have been associated with an allelic variant of Huntington disease (OMIM#606438), in which developmental impairment, including neurologic abnormalities and dysarthria, are featured (Seixas et al., 2012, Mariani et al., 2016). Likewise, mutations in *JPH3* give rise to generalized cerebral atrophy, mostly impacting on the basal ganglia (a core component of the brain language circuitry), and are associated with cognitive decline and psychiatric features, including lack of speech due to akinexia (Walker et al., 2003, Schneider et al., 2012).

Also *ABCG1* has been associated with conditions entailing cognitive impairment, language deficits, and neuropsychiatric symptoms (Leoni and Caccia 2015).

CACNA1D is associated with several neuropsychiatric conditions (Kabir et al., 2016) and plays important roles in hippocampus-dependent learning and memory (Marschallinger et al., 2015). It also contributes to aversive learning and memory processes (Berger and Bartsch 2014, Liu et al., 2014), and has been linked to neurodegenerative disorders (Berger and Bartsch 2014). Mutations in this gene are considered among risk factors for ASD and intellectual disability, both entailing language deficits (Pinggera et al., 2015).

HES1 is thought to be important for the evolution of language, because of its specific interactions with *ROBO1* and *RUNX2* (Boeckx and Benítez-Burraco, 2014b).

POMT1 is associated with clinical conditions entailing severe mental retardation (van Reeuwijk et al 2006, Godfrey et al., 2007, Yang et al., 2016. Mutations in this gene occasionally result in psychotic symptoms (hallucinatory behavior) (Haberlova et al 2014).

TBX1 and *CRKL* map within the chromosomal hotspot for the Di George/velocardiofacial clinical spectrum, which are neurocristopathies entailing brain anomalies, behavioural disturbances, cognitive impairment, and language delay (Swillen et al., 1997, Swillen et al., 1999, Guris et al., 2001, Glaser et al., 2002). Tbx1 haploinsufficiency in mice causes prepulse inhibition, a robust endophenotype of nonsyndromic SZ (Paylor et al., 2006), and impacts negatively on pup-mother social communication (Takahashi et al., 2016).

Polymorphisms in *NEUROG1* have been associated with SZ and schizoaffective disorder, one of which being significantly associated with increased cerebral gray matter and generalized cognitive deficits (Ho et al., 2008).

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

SYNJ2 is an evolutionary conserved gene, and a putative cognitive candidate, whose variants have been found associated with cognitive ageing in selected populations (López et al., 2012).

Finally, mutations in *GFAP* give rise to Alexander disease (OMIM#203450). Specifically, *GFAP* is upregulated in the left posterior superior temporal gyrus (Wernicke's area) of schizophrenics, a region crucially implicated in language processing (Martins de Souza et al., 2009).

The involvement of most of these common candidates for SZ, domestication and NC in language function provides with an unexpected, intriguing window on language evolution. As we pointed out in the introductory section, an evolutionary link has been claimed to exist between the origins of language and the prevalence of SZ among human populations, because of the nature of the brain changes that brought about language, which plausibly favour the dysfunctions typically found in SZ. In this paper we have argued for putting the focus not only on the split between extinct hominins and AMHs, but also on the time period following the emergence of our species. The main reason is that changes in the social environment linked to our subsequent self-domestication are expected to have contributed to the emergence of modern languages. As we have showed in the paper, many candidates for domestication and NC development and function are involved in language, but also in the etiopathogenesis of SZ, reinforcing the view that domestication, language evolution, and SZ are intimately related. The genes we highlight here might have contributed to this set of late, domestication-related changes in the human phenotype. Interestingly, signals of ancient selection (occurring >1,900 generations ago, prior to the split of present-day human groups) have been found in some of our candidates, particularly, in *ZEB2*, but also in *BMPR2*, a gene encoding another BMP receptor (Zhou et al., 2015). This is in line with the finding that SZ risk alleles may have mainly appeared during this late period, after the emergence of our species. We expect that these recent changes in our candidates contributed as well to the changes that are concomitant to the domestication process.

6. Conclusions

Taken together, the data discussed in this paper may provide original hints towards the clarification of some aspect of SZ etiopathogenesis, balancing genetic, epigenetic and environmental factors, and merging development and evolution. The proposed approach may help to disentangle as well the evolutionary history of human cognition, and specifically, of the human faculty of language. In particular, it supports the view that changes in the social context linked to self-domestication contributed decisively to the emergence of modern language and present-day complex languages and that both genetic and environmental factors play a role in this process.

Acknowledgements

Preparation of this work was supported in part by funds from the Spanish Ministry of Economy and Competitiveness (grant numbers FFI2014-61888-EXP and FFI-2013-43823-P to ABB), and in part by "Linea D1- 2016 and 17" intramural funds from Università Cattolica S. Cuore (to WL).

Conflicts of interest

The authors declare no conflict of interest.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

References

Aberg KA, McClay JL, Nerella S, Clark S, Kumar G, Chen W, Khachane AN, Xie L, Hudson A, Gao G, Harada A, Hultman CM, Sullivan PF, Magnusson PK, van den Oord EJ (2014): Methylome-wide association study of schizophrenia: identifying blood biomarker signatures of environmental insults. JAMA Psychiatry 71(3):255-64.

Adam MP, Schelley S, Gallagher R, Brady AN, Barr K, Blumberg B, Shieh JT, Graham J, Slavotinek A, Martin M, Keppler-Noreuil K, Storm AL, Hudgins L (2006): Clinical features and management issues in Mowat-Wilson syndrome. Am J Med Genet A 140:2730-41.

Akabaliev VH, Sivkov ST, Mantarkov MJ, Ahmed-Popova FM (2011): Biomarker profile of minor physical anomalies in schizophrenia patients. Folia Med (Plovdiv) 53:45-51.

Aksoy-Poyraz C, Poyraz BÇ, Turan Ş, Arikan MK (2011): Minor physical anomalies and neurological soft signs in patients with schizophrenia and their siblings. Psychiatry Res 190:85-90.

Alappat S, Zhang ZY, Chen YP (2003): Msx homeobox gene family and craniofacial development. Cell Res 13:429-42.

Albert FW, Somel M, Carneiro M, Aximu-Petri A, Halbwax M, Thalmann O, Blanco-Aguiar JA, Plyusnina IZ, Trut L, Villafuerte R, Ferrand N, Kaiser S, Jensen P, Pääbo S (2012): A comparison of brain gene expression levels in domesticated and wild animals. PLoS Genet 8: e1002962.

Allen T, Willard VW, Anderson LM, Hardy KK, Bonner MJ (2016): Social functioning and facial expression recognition in children with neurofibromatosis type 1. J Intellect Disabil Res 60:282-93.

Amato R, Pinelli M, Monticelli A, Miele G, Cocozza S (2010): Schizophrenia and vitamin D related genes could have been subject to latitude-driven adaptation. BMC Evol Biol 10:351.

Anderson JL, Gutmann DH (2015): Neurofibromatosis type 1. Handb Clin Neurol 132:75-86.

Attanasio C, Nord AS, Zhu Y, Blow MJ, Li Z, Liberton DK, Morrison H, Plajzer-Frick I, Holt A, Hosseini R, Phouanenavong S, Akiyama JA, Shoukry M, Afzal V, Rubin EM, FitzPatrick DR, Ren B, Hallgrímsson B, Pennacchio LA, Visel A (2013): Fine tuning of craniofacial morphology by distant-acting enhancers. Science 342(6157):1241006.

Au PY, Racher HE, Graham JM Jr, Kramer N, Lowry RB, Parboosingh JS, Innes AM, FORGE Canada Consortium (2014): De novo exon 1 missense mutations of SKI and Shprintzen-Goldberg syndrome: two new cases and a clinical review. Am J Med Genet A 164A:676-84.

Ayalew M, Le-Niculescu H, Levey DF, Jain N, Changala B, Patel SD, Winiger E, Breier A, Shekhar A, Amdur R, Koller D, Nurnberger JI, Corvin A, Geyer M, Tsuang MT, Salomon D, Schork NJ, Fanous AH, O'Donovan MC, Niculescu AB (2012): Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction. Mol Psychiatry 17(9):887-905.

Baranek C, Atanasoski S (2012): Modulating epigenetic mechanisms: the diverse functions of Ski during cortical development. Epigenetics 7: 676-9.

Baribeau DA, Anagnostou E (2013): A comparison of neuroimaging findings in childhood onset schizophrenia and autism spectrum disorder: a review of the literature. Front Psychiatry 4:175.

Barnes MR, Huxley-Jones J, Maycox PR, Lennon M, Thornber A, Kelly F, Bates S, Taylor A, Reid J, Jones N, Schroeder J, Scorer CA, Davies C, Hagan JJ, Kew JN, Angelinetta C, Akbar T, Hirsch S, Mortimer AM, Barnes TR, de Belleroche J (2011): Transcription and pathway analysis of the superior temporal cortex and anterior prefrontal cortex in schizophrenia. J Neurosci Res 89:1218-27.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Beckmann H, Lang RE, Gattaz WF (1985): Vasopressin–oxytocin in cerebrospinal fluid of schizophrenic patients and normal controls. Psychoneuroendocrinology 10: 187–191. Bedi U, Mishra VK, Wasilewski D, Scheel C, Johnsen SA (2014): Epigenetic plasticity: a central regulator of epithelial-to-mesenchymal transition in cancer. Oncotarget 5(8):2016-29.

Benítez-Burraco A (2016): A biolinguistic approach to sign languages; in Marschark M, Spencer PE (eds): The Oxford Handbook of Deaf Studies: Language and Language Development. Oxford, Oxford University Press, pp. 247-263.

Benítez-Burraco A, Boeckx C (2015): Possible functional links among brain- and skull-related genes selected in modern humans. Front Psychol 6:794.

Benítez-Burraco A, Lattanzi W, Murphy E (2016): Language impairments in ASD resulting from a failed domestication of the human brain. Front Neurosci 10:373.

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

Berger SM, Bartsch D (2014): The role of L-type voltage-gated calcium channels Cav1.2 and Cav1.3 in normal and pathological brain function. Cell Tissue Res 357:463-76.

Bertelsen B, Melchior L, Jensen LR, Groth C, Glenthøj B, Rizzo R, Debes NM, Skov L, Brøndum-Nielsen K, Paschou P, Silahtaroglu A, Tümer Z (2014): Intragenic deletions affecting two alternative transcripts of the IMMP2L gene in patients with Tourette syndrome. Eur J Hum Genet 22:1283-9.

Bigdeli TB, Ripke S, Bacanu SA, Lee SH, Wray NR, Gejman PV, Rietschel M, Cichon S, St Clair D, Corvin A, Kirov G, McQuillin A, Gurling H, Rujescu D, Andreassen OA, Werge T, Blackwood DH, Pato CN, Pato MT, Malhotra AK, O'Donovan MC, Kendler KS, Fanous AH, Schizophrenia Working Group of the Psychiatric Genomics Consortium (2016): Genome-wide association study reveals greater polygenic loading for schizophrenia in cases with a family history of illness. Am J Med Genet B Neuropsychiatr Genet 171B(2):276-89.

Boeckx C, Benítez-Burraco A (2014a): The shape of the human language-ready brain. Front Psychol 5:282.

Boeckx C, Benítez-Burraco A (2014b): Globularity and language-readiness: Generating new predictions by expanding the set of genes of interest. Front Psychol 5:1324.

Boyd PJ, Cunliffe VT, Roy S, Wood JD (2015): Sonic hedgehog functions upstream of disrupted-in-schizophrenia 1 (disc1): implications for mental illness. Biol Open 4:1336-43.

Boyle MI, Jespersgaard C, Brøndum-Nielsen K, Bisgaard AM, Tümer Z (2015): Cornelia de Lange syndrome. Clin Genet 88:1-12.

Bozdagi O, Wang XB, Nikitczuk JS, Anderson TR, Bloss EB, Radice GL, Zhou Q, Benson DL, Huntley GW (2010): Persistence of coordinated long-term potentiation and dendritic spine enlargement at mature hippocampal CA1 synapses requires N-cadherin. J Neurosci 30: 9984-9.

Bradley AJ, Dinan TG (2010): A systematic review of hypothalamic-pituitary-adrenal axis function in schizophrenia: implications for mortality. J Psychopharmacol 24(4 Suppl):91-118.

Brei NG, Klein-Tasman BP, Schwarz GN, Casnar CL (2014): Language in young children with neurofibromatosis-1: relations to functional communication, attention, and social functioning. Res Dev Disabil 35:2495-504.

Brown AS (2011): The environment and susceptibility to schizophrenia. Prog Neurobiol. 93:23-58.

Brüne M (2004): Schizophrenia-an evolutionary enigma? Neurosci Biobehav Rev 28:41-53.

Bury LA, Sabo SL (2014): Dynamic mechanisms of neuroligin-dependent presynaptic terminal assembly in living cortical neurons. Neural Dev. 29;9:13.

Cannon M, Jones PB, Murray RM (2002): Obstetric complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry 159:1080-92.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Caronia G, Wilcoxon J, Feldman P, Grove EA (2010): Bone morphogenetic protein signaling in the developing telencephalon controls formation of the hippocampal dentate gyrus and modifies fear-related behavior. J Neurosci 30: 6291-301.

Castellano S, Parra G, Sánchez-Quinto FA, Racimo F, Kuhlwilm M, Kircher M, Sawyer S, Fu Q, Heinze A, Nickel B, Dabney J, Siebauer M, White L, Burbano HA, Renaud G, Stenzel U, Lalueza-Fox C, de la Rasilla M, Rosas A, Rudan P, Brajković D, Kucan Ž, Gušic I, Shunkov MV, Derevianko AP, Viola B, Meyer M, Kelso J, Andrés AM, Pääbo S (2014): Patterns of coding variation in the complete exomes of three Neandertals. Proc Natl Acad Sci USA 111:6666-6671.

Chang L, Kessler DS (2010): Foxd3 is an essential Nodal-dependent regulator of zebrafish dorsal mesoderm development. Dev Biol 342:39-50.

Chen C, Cheng L, Grennan K, Pibiri F, Zhang C, Badner JA, Members of the Bipolar Disorder Genome Study (BiGS) Consortium, Gershon ES, Liu C (2013): Two gene co-expression modules differentiate psychotics and controls. Mol Psychiatry 18:1308-14. Cheung M, Briscoe J (2003): Neural crest development is regulated by the transcription factor Sox9. Development 130(23):5681-93.

Cho KK, Hoch R, Lee A, T, Patel T, Rubenstein JL, Sohal VS (2015): Gamma rhythms link prefrontal interneuron dysfunction with cognitive inflexibility in Dlx5/6(+/-) mice. Neuron 85:1332-43.

Christophersen NS, Grønborg M, Petersen TN, Fjord-Larsen L, Jørgensen JR, Juliusson B, Blom N, Rosenblad C, Brundin P (2007): Midbrain expression of Delta-like 1 homologue is regulated by GDNF and is associated with dopaminergic differentiation. Exp Neurol 204(2):791-801.

Ciufolini S, Dazzan P, Kempton MJ, Pariante C, Mondelli V (2014): HPA axis response to social stress is attenuated in schizophrenia but normal in depression: evidence from a meta-analysis of existing studies. Neurosci Biobehav Rev 47:359-68.

Clarke DJ, Buckley ME (1989): Familial association of albinism and schizophrenia. Br J Psychiatry 155:551-3.

Cohen MM Jr (2000): Craniofacial disorders caused by mutations in homeobox genes MSX1 and MSX2. J Craniofac Genet Dev Biol 20:19-25.

Compton MT, Bollini AM, McKenzie Mack L, Kryda AD, Rutland J, Weiss PS, Bercu Z, Esterberg ML, Walker EF (2007): Neurological soft signs and minor physical anomalies in patients with schizophrenia and related disorders, their first-degree biological relatives, and non-psychiatric controls. Schizophr Res 94:64-73.

Coulpier M, Anders J, Ibáñez CF (2002): Coordinated activation of autophosphorylation sites in the RET receptor tyrosine kinase: importance of tyrosine 1062 for GDNF mediated neuronal differentiation and survival. J Biol Chem 277(3):1991-9.

Crespi B, Badcock C (2008): Psychosis and autism as diametrical disorders of the social brain. Behav Brain Sci 31:241-320.

Crow TJ (2000): Schizophrenia as the price that homo sapiens pays for language: a resolution of the central paradox in the origin of the species. Brain Res Brain Res Rev. 31:118-29.

Darrell-Berry H, Berry K, Bucci S (2016): The relationship between paranoia and aggression in psychosis: A systematic review. Schizophr Res 172:169-76. Darwin C (1871): The Descent of Man, and Selection in Relation to Sex. London, John Murray.

Datta D, Arion D, Corradi JP, Lewis DA (2015): Altered expression of CDC42 signaling pathway components in cortical layer 3 pyramidal cells in schizophrenia. Biol Psychiatry 78:775-85.

Davis MC, Green MF, Lee J, Horan WP, Senturk D, Clarke AD, Marder SR (2014): Oxytocin-augmented social cognitive skills training in schizophrenia. Neuropsychopharmacology 39: 2070–2077. de Baumont A, Maschietto M, Lima L, Carraro DM, Olivieri EH, Fiorini A,

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Barreta LA, Palha JA, Belmonte-de-Abreu P, Moreira Filho CA, Brentani H (2015): Innate immune response is differentially dysregulated between bipolar disease and schizophrenia. Schizophr Res 161:215-21. De Peri L, Crescini A, Deste G, Fusar-Poli P, Sacchetti E, Vita A (2012): Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. Curr Pharm Des 18:486-94

Deacon TW (2009): Relaxed selection and the role of epigenesis in the evolution of language; In Blumberg M, Freeman J, Robinson J (eds): Oxford Handbook of Developmental Behavioral Neuroscience. New York, Oxford University Press, pp. 730-752.

Deutsch CK, Levy DL, Price SF, Bodkin JA, Boling L, Coleman MJ, Johnson F, Lerbinger J, Matthysse S, Holzman PS (2015): Quantitative measures of craniofacial dysmorphology in a family study of schizophrenia and bipolar illness. Schizophr Bull 41:1309-16. Dominguez MH, Ayoub AE, Rakic P (2013): POU-III transcription factors (Brn1, Brn2, and Oct6) influence neurogenesis, molecular identity, and migratory destination of upper-layer cells of the cerebral cortex. Cereb Cortex 23:2632-43.

Drerup CM, Wiora HM, Topczewski J, Morris JA (2009): Disc1 regulates foxd3 and sox10 expression, affecting neural crest migration and differentiation. Development 136(15):2623-32.

Escot S, Blavet C, Faure E, Zaffran S, Duband JL, Fournier-Thibault C (2016): Disruption of CXCR4 signaling in pharyngeal neural crest cells causes DiGeorge syndrome-like malformations. Development 143:582-8.

Feifel D, Macdonald K, Cobb P, Minassian A (2012): Adjunctive intranasal oxytocin improves verbal memory in people with schizophrenia. Schizophr Res 139:207–210. Ferrarelli F, Sarasso S, Guller Y, Riedner BA, Peterson MJ, Bellesi M, Massimini M, Postle BR, Tononi G (2012): Reduced natural oscillatory frequency of frontal thalamocortical circuits in schizophrenia. Arch Gen Psychiatry 69:766-774.

Feifel D, Macdonald K, Nguyen A, Cobb P, Warlan H, Galangue B, Minassian A, Becker O, Cooper J, Perry W, Lefebvre M, Gonzales J, Hadley A (2010): Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. Biol Psychiatry 68:678–680.

Filová B, Ostatníková D, Celec P, Hodosy J (2013): The effect of testosterone on the formation of brain structures. Cells Tissues Organs 197:169-77.

Fisher SE, Francks C, Marlow AJ, MacPhie IL, Newbury DF, Newbury DF, Cardon LR, Ishikawa-Brush Y, Richardson AJ, Talcott JB, Gayán J, Olson RK, Pennington BF, Smith SD, DeFries JC, Stein JF, Monaco AP. (2002): Independent genome-wide scans identify a chromosome 18 quantitative-trait locus influencing dyslexia. Nat Genet 30:86–91.

Frank SM. (1978): Psycholinguistic findings in Gilles de la Tourette syndrome. J Commun Disord 11:349-63.

Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, Georgieva L, Rees E, Palta P, Ruderfer DM, Carrera N, Humphreys I, Johnson JS, Roussos P, Barker DD, Banks E, Milanova V, Grant SG, Hannon E, Rose SA, Chambert K, Mahajan M, Scolnick EM, Moran JL, Kirov G, Palotie A, McCarroll SA, Holmans P, Sklar P, Owen MJ, Purcell SM, O'Donovan MC (2014): De novo mutations in schizophrenia implicate synaptic networks. Nature 506(7487):179-84.

Garavelli L, Ivanovski I, Caraffi SG, Santodirocco D, Pollazzon M, Cordelli DM, Abdalla E, Accorsi P, Adam MP, Baldo C, Bayat A, Belligni E, Bonvicini F, Breckpot J, Callewaert B, Cocchi G, Cuturilo G, Devriendt K, Dinulos MB, Djuric O, Epifanio R, Faravelli F, Formisano D, Giordano L, Grasso M, Grønborg S, Iodice A, Iughetti L, Lacombe D, Maggi M, Malbora B, Mammi I, Moutton S, Møller R, Muschke P, Napoli M, Pantaleoni C, Pascarella R, Pellicciari A, Poch-Olive ML, Raviglione F, Rivieri F, Russo C, Savasta S, Scarano G, Selicorni A, Silengo M, Sorge G, Tarani L, Tone LG, Toutain A, Trimouille A,

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Valera ET, Vergano SS, Zanotta N, Zollino M, Dobyns WB, Paciorkowski AR (2016): Neuroimaging findings in Mowat-Wilson syndrome: a study of 54 patients. Genet Med doi: 10.1038/gim.2016.176.

Garg S, Plasschaert E, Descheemaeker MJ, Huson S, Borghgraef M, Vogels A, Evans DG, Legius E, Green J (2015): Autism spectrum disorder profile in neurofibromatosis type I. J Autism Dev Disord 45:1649-57. Georgieva L, Moskvina V, Peirce T, Norton N, Bray NJ, Jones L, Holmans P, Macgregor S, Zammit S, Wilkinson J, Williams H, Nikolov I, Williams N, Ivanov D, Davis KL, Haroutunian V, Buxbaum JD, Craddock N, Kirov G, Owen MJ, O'Donovan MC (2006): Convergent evidence that oligodendrocyte lineage transcription factor 2 (OLIG2) and interacting genes influence susceptibility to schizophrenia. Proc Natl Acad Sci U S A 103:12469-74.

Geoffroy PA, Etain B, Houenou J (2013): Gene x environment interactions in schizophrenia and bipolar disorder: evidence from neuroimaging. Front Psychiatry 4: 136.

Gibson CM, Penn DL, Smedley KL, Leserman J, Elliott T, Pedersen CA (2014): A pilot six-week randomized controlled trial of oxytocin on social cognition and social skills in schizophrenia. Schizophr Res 156:261–265.

Gil-Sanz C, Landeira B, Ramos C, Costa MR, Müller U (2014): Proliferative defects and formation of a double cortex in mice lacking Mltt4 and Cdh2 in the dorsal telencephalon. J Neurosci 34: 10475-87.

Gimelli S, Capra V, Di Rocco M, Leoni M, Mirabelli-Badenier M, Schiaffino MC, Fiorio P, Cuoco C, Gimelli G, Tassano E. (2014): Interstitial 7q31.1 copy number variations disrupting IMMP2L gene are associated with a wide spectrum of neurodevelopmental disorders. Mol Cytogenet 7:54.

Girshkin L, O'Reilly N, Quidé Y, Teroganova N, Rowland JE, Schofield PR, Green MJ (2016): Diurnal cortisol variation and cortisol response to an MRI stressor in schizophrenia and bipolar disorder. Psychoneuroendocrinology 67:61-9.

Gitton Y, Benouaiche L, Vincent C, Heude E, Soulika M, Bouhali K, Couly G, Levi G (2011): Dlx5 and Dlx6 expression in the anterior neural fold is essential for patterning the dorsal nasal capsule. Development 138:897-903.

Glaser B, Mumme DL, Blasey C, Morris MA, Dahoun SP, Antonarakis SE, Reiss AL, Eliez S (2002): Language skills in children with velocardiofacial syndrome (deletion 22q11.2). J Pediatr 140:753-8.

Gleeson PC, Worsley R, Gavrilidis E, Nathoo S, Ng E, Lee S, Kulkarni J (2016): Menstrual cycle characteristics in women with persistent schizophrenia. Aust N Z J Psychiatry 50:481-7. Glessner JT, Reilly MP, Kim CE, Takahashi N, Albano A, Hou C, Bradfield JP, Zhang H, Sleiman PM, Flory JH, Imielinski M, Frackelton EC, Chiavacci R, Thomas KA, Garris M, Otieno FG, Davidson M, Weiser M, Reichenberg A, Davis KL, Friedman JI, Cappola TP, Margulies KB, Rader DJ, Grant SF, Buxbaum JD, Gur RE, Hakonarson H (2010): Strong synaptic transmission impact by copy number variations in schizophrenia. Proc Natl Acad Sci U S A. 107(23):10584-9.

Glovinsky D, Kalogeras KT, Kirch DG, Suddath R, Wyatt RJ (1994): Cerebrospinal fluid oxytocin concentration in schizophrenic patients does not differ from control subjects and is not changed by neuroleptic medication. Schizophr Res 11:273-6.

Godfrey C, Clement E, Mein R, Brockington M, Smith J, Talim B, Straub V, Robb S, Quinlivan R, Feng L, Jimenez-Mallebrera C, Mercuri E, Manzur AY, Kinali M, Torelli S, Brown SC, Sewry CA, Bushby K, Topaloglu H, North K, Abbs S, Muntoni F (2007): Refining genotype phenotype correlations in muscular dystrophies with defective glycosylation of dystroglycan. Brain 130: 2725-35.

Gogos A, Sbisa AM, Sun J, Gibbons A, Udawela M, Dean B (2015): A Role for Estrogen in Schizophrenia: Clinical and Preclinical Findings. Int J Endocrinol 2015:615356.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Gokhman D, Lavi E, Prüfer K, Fraga MF, Riancho JA, Kelso J, Pääbo S, Meshorer E, Carmel L (2014): Reconstructing the DNA methylation maps of the Neandertal and the Denisovan. Science 344:523-527.

Goldberg TE, Weinberger DR (2004): Genes and the parsing of cognitive processes. Trends Cogn Sci 8: 325-35

González-Giraldo Y, Rojas J, Novoa P, Mueller ST, Piper BJ, Adan A, Forero DA (2014): Functional polymorphisms in BDNF and COMT genes are associated with objective differences in arithmetical functioning in a sample of young adults. Neuropsychobiology 70: 152-7.

Gourion D, Goldberger C, Bourdel MC, Jean Bayle F, Lôo H, Krebs MO (2004): Minor physical anomalies in patients with schizophrenia and their parents: prevalence and pattern of craniofacial abnormalities. Psychiatry Res 125:21-8.

Gunnar MR, Wewerka S, Frenn K, Long JD, Griggs C (2009): Developmental changes in hypothalamus-pituitary-adrenal activity over the transition to adolescence: normative changes and associations with puberty. Dev Psychopathol 21:69-85.

Gunnell D, Rasmussen F, Fouskakis D, Tynelius P, Harrison G (2003): Patterns of fetal and childhood growth and the development of psychosis in young males: A cohort study. Am J Epidemiol 158:291–300.

Guris DL, Fantes J, Tara D, Druker BJ, Imamoto A (2001): Mice lacking the homologue of the human 22q11.2 gene CRKL phenocopy neurocristopathies of DiGeorge syndrome. Nat Genet 27:293-8.

Haberlova J, Mitrović Z, Zarković K, Lovrić D, Barić V, Berlengi L, Bilić K, Fumić K, Kranz K, Huebner A, von der Hagen M, Barresi R, Bushby K, Straub V, Barić I, Lochmüller H (2014): Psycho-organic symptoms as early manifestation of adult onset POMT1-related limb girdle muscular dystrophy. Neuromuscul Disord 24:990-2.

Haddad-Tóvolli R, Heide M, Zhou X, Blaess S, Álvarez-Bolado G (2012): Mouse thalamic differentiation: gli-dependent pattern and gli-independent prepattern. Front Neurosci 6:27.

Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS (2013): Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr Bull 39:1129-38. Hajnal A, Csábi G, Herold R, Jeges S, Halmai T, Trixler D, Simon M, Tóth ÁL, Tényi T (2016): Minor physical anomalies are more common among the first-degree unaffected relatives of schizophrenia patients - Results with the Méhes Scale. Psychiatry Res 237:224-8.

Han J, Ishii M, Bringas P Jr, Maas RL, Maxson RE Jr, Chai Y (2007): Concerted action of Msx1 and Msx2 in regulating cranial neural crest cell differentiation during frontal bone development. Mech Dev 124: 729-45.

Hannula-Jouppi K, Kaminen-Ahola N, Taipale M, Eklund R, Nopola-Hemmi J, Kääriäinen H, Kere J (2005): The axon guidance receptor gene ROBO1 is a candidate gene for developmental dyslexia. PLoS Genetics 1:e50.

Hare B, Tomasello M (2005): Human-like social skills in dogs? Trends Cogn Sci 9:439-444.

Hata K, Iida J, Iwasaka H, Negoro HI, Ueda F, Kishimoto T (2003): Minor physical anomalies in childhood and adolescent onset schizophrenia. Psychiatry Clin Neurosci 57:17-21.

Hattori T, Shimizu S, Koyama Y, Emoto H, Matsumoto Y, Kumamoto N, Yamada K, Takamura H, Matsuzaki S, Katayama T, Tohyama M, Ito A (2014): DISC1 (disrupted-in-schizophrenia-1) regulates differentiation of oligodendrocytes. PLoS One 9,e88506.

Haukka J, Suvisaari J, Häkkinen L, Lönnqvist J (2008): Growth pattern and risk of schizophrenia. Psychol Med 38:63-70.

Haukvik UK, Hartberg CB, Agartz I (2013): Schizophrenia--what does structural MRI show? Tidsskr Nor Laegeforen 133:850-3. Havelka D, Prikrylova-Kucerova H, Prikryl R, Ceskova

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

E (2016): Cognitive impairment and cortisol levels in first-episode schizophrenia patients. Stress 19:383-9.

Hecht EE, Gutman DA, Preuss TM, Sánchez MM, Parr LA, Rilling JK (2013): Process versus product in social learning: comparative diffusion tensor imaging of neural systems for action execution-observation matching in macaques, chimpanzees, and humans. Cortex 23:1014-1024.

Hegarty SV, Sullivan AM, O'Keeffe GW (2015): Zeb2: A multifunctional regulator of nervous system development. Prog Neurobiol 132: 81-95.

Hempel RJ, Tulen JH, van Beveren NJ, Röder CH, de Jong FH, Hengeveld MW (2010): Diurnal cortisol patterns of young male patients with schizophrenia. Psychiatry Clin Neurosci 64:548-54.

Hetz S, Acikgoez A, Voss U, Nieber K, Holland H, Hegewald C, Till H, Metzger R, Metzger M (2014): In vivo transplantation of neurosphere-like bodies derived from the human postnatal and adult enteric nervous system: a pilot study. PLoS One 9(4):e93605.

Hinzen W, Rosselló J (2015): The linguistics of schizophrenia: thought disturbance as language pathology across positive symptoms. Front Psychol 6:971.

Hirayasu Y, Shenton ME, Salisbury DF, Dickey CC, Fischer IA, Mazzoni P, Kisler T, Arakaki H, Kwon JS, Anderson JE, Yurgelun-Todd D, Tohen M, McCarley RW (1998): Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first episode affective disorder and normal subjects. Am J Psychiatry 155:1384-1391.

Ho BC, Epping E, Wang K, Andreasen NC, Librant A, Wassink TH (2008): Basic helix-loop-helix transcription factor NEUROG1 and schizophrenia: effects on illness susceptibility, MRI brain morphometry and cognitive abilities. Schizophr Res 106:192-9.

Hochman KM, Lewine RR (2004): Age of menarche and schizophrenia onset in women. Schizophr Res 69:183-8.

Iannuzzi S, Albaret JM, Chignac C, Faure-Marie N, Barry I, Karsenty C, Chaix Y (2016): Motor impairment in children with Neurofibromatosis type 1: Effect of the comorbidity with language disorders. Brain Dev 38:181-7.

Ismail B, Cantor-Graae E, McNeil TF (1998): Minor physical anomalies in schizophrenic patients and their siblings. Am J Psychiatry 155:1695-702.

Iwashiro N, Koike S, Satomura Y, Suga M, Nagai T, Natsubori T, Tada M, Gonoi W, Takizawa R, Kunimatsu A, Yamasue H, Kasai K (2016): Association between impaired brain activity and volume at the sub-region of Broca's area in ultra-high risk and first-episode schizophrenia: A multi-modal neuroimaging study. Schizophr Res 172:9-15.

Jasińska KK, Molfese PJ, Kornilov SA, Mencl WE, Frost SJ, Lee M, Pugh KR, Grigorenko EL, Landi N (2016): The BDNF Val66Met polymorphism influences reading ability and patterns of neural activation in children. PLoS One 11:e0157449.

Jing J, Ren Y, Zong Z, Liu C, Kamiya N, Mishina Y, Liu Y, Zhou X, Feng JQ (2013): BMP receptor 1A determines the cell fate of the postnatal growth plate. Int J Biol Sci 9(9):895-906.

Jing S, Wen D, Yu Y, Holst PL, Luo Y, Fang M, Tamir R, Antonio L, Hu Z, Cupples R, Louis JC, Hu S, Altrock BW, Fox GM (1996): GDNF-induced activation of the ret protein tyrosine kinase is mediated by GDNFR-alpha, a novel receptor for GDNF. Cell 85(7):1113-24.

Jones EG, Rubenstein JLR (2004): Expression of regulatory genes during differentiation of thalamic nuclei in mouse and monkey. J Comp Neurol 477:55-80.

Kabir ZD, Lee AS, Rajadhyaksha AM (2016): L-type Ca2+ channels in mood, cognition and addiction: integrating human and rodent studies with a focus on behavioural endophenotypes. J Physiol 594:5823-5837.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Kadowaki M, Nakamura S, Machon O, Krauss S, Radice GL, Takeichi M (2007): N-cadherin mediates cortical organization in the mouse brain. Dev Biol 304: 22-33.

Kagawa, H, Yamada, H., Lin, R-S, Mizuta, T, Hasegawa T, Okanoya K (2012): Ecological correlates of song complexity in white-rumped munias: the implication of relaxation of selection as a cause for signal variation in birdsong. Interact Stud 13:263-284.

Kebir O, Mouaffak F, Chayet M, Leroy S, Tordjman S, Amado I, Krebs MO (2009): Semantic but not phonological verbal fluency associated with BDNF Val66Met polymorphism in schizophrenia. Am J Med Genet B Neuropsychiatr Genet 150B:441-2. Khadka D, Luo T, Sargent TD (2006): Msx1 and Msx2 have shared essential functions in neural crest but may be dispensable in epidermis and axis formation in Xenopus. Int J Dev Biol 50:499-502.

Keller A, Castellanos FX, Vaituzis AC, Jeffries NO, Giedd JN, Rapoport JL (2003): Progressive loss of cerebellar volume in childhood-onset schizophrenia. Am J Psychiatry 160: 128-33.

Kielar C, Wishart TM, Palmer A, Dihanich S, Wong AM, Macauley SL, Chan CH, Sands MS, Pearce DA, Cooper JD, Gillingwater TH (2009): Molecular correlates of axonal and synaptic pathology in mouse models of Batten disease. Hum Mol Genet 18:4066-80.

Kircher TT, Oh TM, Brammer MJ, McGuire PK (2005): Neural correlates of syntax production in schizophrenia. Br J Psychiatry 186: 209-14.

Kraus P, Lufkin T (2006): Dlx homeobox gene control of mammalian limb and craniofacial development. Am J Med Genet A 140:1366-1374.

Krishnan S, Watkins KE, Bishop DV (2016): Neurobiological basis of language learning difficulties. Trends Cogn Sci 20: 701-14.

Lamminranta S, Aberg LE, Autti T, Moren R, Laine T, Kaukoranta J, Santavuori P. (2001): Neuropsychological test battery in the follow-up of patients with juvenile neuronal ceroid lipofuscinosis. J Intellect Disabil Res 45:8-17.

Lanz TA, Guilmette E, Gosink MM, Fischer JE, Fitzgerald LW, Stephenson DT, Pletcher MT (2013): Transcriptomic analysis of genetically defined autism candidate genes reveals common mechanisms of action. Mol Autism 15;4(1):45.

Lapierre D, Braun CM, Hodgins S, Toupin J, Léveillée S, Constantineau C (1995): Neuropsychological correlates of violence in schizophrenia. Schizophr Bull 21:253-62.

Lattanzi W (2016): Molecular genetics of craniosynostosis. eLS. John Wiley & Sons, Ltd: Chichester. doi: 10.1002/9780470015902.a0025186

Lattanzi W, Barba M, Di Pietro L, Boyadjiev SA. Genetic advances in craniosynostosis. Am J Med Genet A doi: 10.1002/ajmg.a.38159.

Ledda F, Paratcha G, Sandoval-Guzman T, Ibanez CF (2007): GDNF and GFR alpha 1 promote formation of neuronal synapses by ligand-induced cell adhesion. Nat Neurosci 10:293–300.

Leoni V, Caccia C (2015): The impairment of cholesterol metabolism in Huntington disease. Biochim Biophys Acta 1851:1095-105.

Li J, Wilkinson B, Clementel VA, Hou J, O'Dell TJ, Coba MP (2016): Long-term potentiation modulates synaptic phosphorylation networks and reshapes the structure of the postsynaptic interactome. Sci Signal 9:rs8. Li N, Bartlett CW (2012): Defining the genetic architecture of human developmental language impairment. Life Sci 90:469-75.

Li X, Black M, Xia S, Zhan C, Bertisch HC, Branch CA, DeLisi LE (2015): Subcortical structure alterations impact language processing in individuals with schizophrenia and those at high genetic risk. Schizophr Res 169:76-82.

Li X, Branch CA, DeLisi LE (2009): Language pathway abnormalities in schizophrenia: a review of fMRI and other imaging studies. Curr Opin Psychiatry 22:131-9.

Liang J, Von den Hoff J, Lange J, Ren Y, Bian Z, Carels CE (2016): MSX1 mutations and associated disease phenotypes: genotype-phenotype relations. Eur J Hum Genet 24:1663-1670.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Liberg B, Rahm C, Panayiotou A, Pantelis C (2016): Brain change trajectories that differentiate the major psychoses. Eur J Clin Invest 46:658-74. Lin Y, Ma X, Deng W, Han Y, Li M, Liu X, Loh el-W, Li T (2012): Minor physical anomalies in patients with schizophrenia in a Chinese population. Psychiatry Res 200:223-7.

Link AS, Kurinna S, Havlicek S, Lehnert S, Reichel M, Kornhuber J, Winner B, Huth T, Zheng F, Werner S, Alzheimer C (2016): Kdm6b and Pmepa1 as targets of bioelectrically and behaviorally induced activin A signaling. Mol Neurobiol 53: 4210-25.

Liu JA, Wu MH, Yan CH, Chau BK, So H (2013): Phosphorylation of Sox9 is required for neural crest delamination and is regulated downstream of BMP and canonical Wnt signalling. Proc Natl Acad Sci USA 110:2882–2887.

Liu Y, Harding M, Pittman A, Dore J, Striessnig J, Rajadhyaksha A, Chen X (2014): Cav1.2 and Cav1.3 L-type calcium channels regulate dopaminergic firing activity in the mouse ventral tegmental area. J Neurophysiol 112:1119-30. Lopez LM, Harris SE, Luciano M, Liewald D, Davies G, Gow AJ, Tenesa A, Payton A, Ke X, Whalley LJ, Fox H, Haggerty P, Ollier W, Pickles A, Porteous DJ, Horan MA, Pendleton N, Starr JM, Deary IJ (2012): Evolutionary conserved longevity genes and human cognitive abilities in elderly cohorts. Eur J Hum Genet 20:341-7.

Lorenzo J, Barton B, Arnold SS, North KN (2013): Cognitive features that distinguish preschool-age children with neurofibromatosis type 1 from their peers: a matched case-control study. J Pediatr 163:1479-83.e1. Lorenzo J, Barton B, Arnold SS, North KN (2015): Developmental trajectories of young children with neurofibromatosis type 1: a longitudinal study from 21 to 40 months of age. J Pediatr 166:1006-12.e1.

Lupyan G, Dale R (2010): Language structure is partly determined by social structure. PLoS One 5:e8559.

Lyons GE, Micales BK, Herr MJ, Horrigan SK, Namciu S, Shardy D, Stavnezer E (1994): Protooncogene c-ski is expressed in both proliferating and postmitotic neuronal populations. Dev Dyn 201: 354-65.

Mariani LL, Tesson C, Charles P, Cazeneuve C, Hahn V, Youssov K, Freeman L, Grabli D, Roze E, Noël S, Peuvion JN, Bachoud-Levi AC, Brice A, Stevanin G, Durr A (2016): Expanding the spectrum of genes involved in Huntington disease using a combined clinical and genetic approach. JAMA Neurol 73:1105-14. Marschallinger J, Sah A, Schmuckermair C, Unger M, Rotheneichner P, Kharitonova M, Waclawiczek A, Gerner P, Jaksch-Bogensperger H, Berger S, Striessnig J, Singewald N, Couillard-Despres S, Aigner L (2015): The L-type calcium channel Cav1.3 is required for proper hippocampal neurogenesis and cognitive functions. Cell Calcium 58:606-16.

Mariën P, Ackermann H, Adamaszek M, Barwood CH, Beaton A, Desmond J, De Witte E, Fawcett AJ, Hertrich I, Küper M, Leggio M, Marvel C, Molinari M, Murdoch BE, Nicolson RI, Schmahmann JD, Stoodley CJ, Thürling M, Timmann D, Wouters E, Ziegler W (2014): Consensus paper: Language and the cerebellum: an ongoing enigma. Cerebellum 13: 386-410.

Martinez-Garay I, Gil-Sanz C, Franco SJ, Espinosa A, Molnár Z, Mueller U (2016): Cadherin 2/4 signaling via PTP1B and catenins is crucial for nucleokinesis during radial neuronal migration in the neocortex. Development 143: 2121-34.

Martins-de-Souza D, Gattaz WF, Schmitt A, Novello JC, Marangoni S, Turck CW, Dias-Neto E (2009): Proteome analysis of schizophrenia patients Wernicke's area reveals an energy metabolism dysregulation. BMC Psychiatry 9:17. Mascheretti S, Riva V, Giorda R, Beri S, Lanzoni LF, Cellino MR, Marino C (2014): KIAA0319 and ROBO1: evidence on association with reading and pleiotropic effects on language and mathematics abilities in developmental dyslexia. J Hum Genet 59: 189-97.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Mauney SA, Pietersen CY, Sonntag KC, Woo TU. (2015): Differentiation of oligodendrocyte precursors is impaired in the prefrontal cortex in schizophrenia. Schizophr Res 169(1-3):374-80.

McDonald-McGinn DM, Feret H, Nah HD, Bartlett SP, Whitaker LA, Zackai EH (2010): Metopic craniosynostosis due to mutations in GLI3: A novel association. Am J Med Genet A 152A:1654-60.

McGrath J, El-Saadi O, Grim V, Cardy S, Chapple B, Chant D, Lieberman D, Mowry B (2002): Minor physical anomalies and quantitative measures of the head and face in patients with psychosis. Arch Gen Psychiatry 59:458-64.

McLarren KW, Litsiou A, Streit A (2003): DLX5 positions the neural crest and preplacode region at the border of the neural plate. Dev Biol 259:34-47.

Michelato A, Bonvicini C, Ventriglia M, Scassellati C, Randazzo R, Bignotti S, Beneduce R, Riva MA, Gennarelli M (2004): 3'UTR (AGG)n repeat of glial cell line-derived neurotrophic factor (GDNF) gene polymorphism in schizophrenia. Neurosci Lett 357:235-7.

Modabbernia A, Rezaei F, Salehi B, Jafarinia M, Ashrafi M, Tabrizi M, Hosseini SM, Tajdini M, Ghaleiha A, Akhondzadeh S (2013): Intranasal oxytocin as an adjunct to risperidone in patients with schizophrenia: an 8-week, randomized, double-blind, placebo-controlled study. CNS Drugs 27: 57–65.

Mølsted K, Boers M, Kjaer I (2010): The morphology of the sella turcica in velocardiofacial syndrome suggests involvement of a neural crest developmental field. Am J Med Genet A 152A:1450-7.

Montano C, Taub MA, Jaffe A, Briem E, Feinberg JI, Trygvadottir R, Idrizi A, Runarsson A, Berndsen B, Gur RC, Moore TM, Perry RT, Fugman D, Sabunciyan S, Yolken RH, Hyde TM, Kleinman JE, Sobell JL, Pato CN, Pato MT, Go RC, Nimgaonkar V, Weinberger DR, Braff D, Gur RE, Fallin MD, Feinberg AP (2016): Association of DNA Methylation Differences With Schizophrenia in an Epigenome-Wide Association Study. JAMA psychiatry 73(5): 506-14.

Moore L, Kyaw M, Vercammen A, Lenroot R, Kulkarni J, Curtis J, O'Donnell M, Carr VJ, Shannon Weickert C, Weickert TW (2013): Serum testosterone levels are related to cognitive function in men with schizophrenia. Psychoneuroendocrinology 38:1717-28.

Moran P, Stokes J, Marr J, Bock G, Desbonnet L, Waddington J, O'Tuathaigh C (2016): Gene × environment interactions in schizophrenia: evidence from genetic mouse models. Neural Plast 2016: 2173748.

Murphy E (2015): The brain dynamics of linguistic computation. Front Psychol 6:1515.

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 connectomopathies: an evolutionary account. Neurosci Biobehav Rev S0149-7634(16)30155-5.

Noroozian M (2014): The role of the cerebellum in cognition: beyond coordination in the central nervous system. Neurol Clin 32: 1081-104.

O'Donovan MC, Norton N, Williams H, Peirce T, Moskvina V, Nikolov I, Hamshere M, Carroll L, Georgieva L, Dwyer S, Holmans P, Marchini JL, Spencer CC, Howie B, Leung HT, Giegling I, Hartmann AM, Möller HJ, Morris DW, Shi Y, Feng G, Hoffmann P, Propping P, Vasilescu C, Maier W, Rietschel M, Zammit S, Schumacher J, Quinn EM, Schulze TG, Iwata N, Ikeda M, Darvasi A, Shifman S, He L, Duan J, Sanders AR, Levinson DF, Adolfsson R, Osby U, Terenius L, Jönsson EG, Cichon S, Nöthen MM, Gill M, Corvin AP, Rujescu D, Gejman PV, Kirov G, Craddock N, Williams NM, Owen MJ; Molecular Genetics of Schizophrenia Collaboration (2009): Analysis of 10 independent samples

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

provides evidence for association between schizophrenia and a SNP flanking fibroblast growth factor receptor 2. Mol Psychiatry 14:30-6.

Okada N, Fukunaga M, Yamashita F, Koshiyama D, Yamamori H, Ohi K, Yasuda Y, Fujimoto M, Watanabe Y, Yahata N, Nemoto K, Hibar DP, van Erp TG, Fujino H, Isobe M, Isomura S, Natsubori T, Narita H, Hashimoto N, Miyata J, Koike S, Takahashi T, Yamasue H, Matsuo K, Onitsuka T, Iidaka T, Kawasaki Y, Yoshimura R, Watanabe Y, Suzuki M, Turner JA, Takeda M, Thompson PM, Ozaki N, Kasai K, Hashimoto R (2016): Abnormal asymmetries in subcortical brain volume in schizophrenia. Mol Psychiatry 21(10):1460-6.

Oliva JL, Rault JL, Appleton B, Lill A (2015): Oxytocin enhances the appropriate use of human social cues by the domestic dog (Canis familiaris) in an object choice task. Anim Cogn. 18:767-75.

Otreba M, Wrześniok D, Beberok A, Rok J, Buszman E (2015): Melanogenesis and antioxidant defense system in normal human melanocytes cultured in the presence of chlorpromazine. Toxicol In Vitro 29:221-7.

Owen MJ, Sawa A, Mortensen PB (2016): Schizophrenia. Lancet 388:86-97.

Palaniyappan L, Mallikarjun P, Joseph V, White TP, Liddle PF (2011): Regional contraction of brain surface area involves three large-scale networks in schizophrenia. Schizophr Res 129:163-8.

Palomino A, Vallejo-Illarramendi A, González-Pinto A, Aldama A, González-Gómez C, Mosquera F, González-García G, Matute C (2006): Decreased levels of plasma BDNF in first-episode schizophrenia and bipolar disorder patients. Schizophr Research 86:321–22.

Parisi L, Di Filippo T, Roccella M (2015): Behavioral phenotype and Autism Spectrum Disorders in Cornelia de Lange syndrome. Ment Illn 7:5988. Paylor R, Glaser B, Mupo A, Ataliotis P, Spencer C, Sobotka A, Sparks C, Choi CH, Oghalai J, Curran S, Murphy KC, Monks S, Williams N, O'Donovan MC, Owen MJ, Scambler PJ, Lindsay E (2006): Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: implications for 22q11 deletion syndrome. Proc Natl Acad Sci U S A 103:7729-34.

Park DH, Hong SJ, Salinas RD, Liu SJ, Sun SW, Sgualdino J, Testa G, Matzuk MM, Iwamori N, Lim DA (2014): Activation of neuronal gene expression by the JMJD3 demethylase is required for postnatal and adult brain neurogenesis. Cell Rep 8: 1290-9.

Payne JM, Porter M, Pride NA, North KN (2016): Theory of mind in children with Neurofibromatosis Type 1. Neuropsychology 30:439-48.

Pearlson GD, Folley BS (2008): Schizophrenia, psychiatric genetics, and Darwinian psychiatry: an evolutionary framework. Schizophr Bull 34:722-33.

Peter B, Wijsman EM, Nato AQ Jr; University of Washington Center for Mendelian Genomics, Matsushita MM, Chapman KL, Stanaway IB, Wolff J, Oda K, Gabo VB, Raskind WH (2016): Genetic candidate variants in two multigenerational families with childhood apraxia of speech. PLoS One 11:e0153864. Petrella LI, Cai Y, Sereno JV, Gonçalves SI, Silva AJ, Castelo-Branco M (2016): Brain and behaviour phenotyping of a mouse model of neurofibromatosis type-1: an MRI/DTI study on social cognition. Genes Brain Behav 15:637-46. Pinggera A, Lieb A, Benedetti B, Lampert M, Monteleone S, Liedl KR, Tuluc P, Striessnig J (2015): CACNA1D de novo mutations in autism spectrum disorders activate Cav1.3 L-type calcium channels. Biol Psychiatry 77:816-22.

Potkin SG, Macciardi F, Guffanti G, Fallon JH, Wang Q, Turner JA, Lakatos A, Miles MF, Lander A, Vawter MP, Xie X (2010): Identifying gene regulatory networks in schizophrenia. Neuroimage 53:839-47.

Potkin SG, Turner JA, Guffanti G, Lakatos A, Fallon JH, Nguyen DD, Mathalon D, Ford J, Lauriello J, Macciardi F, FBIRN (2009): A genome-wide association study of schizophrenia using brain activation as a quantitative phenotype. Schizophr Bull 35:96-108.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Praharaj SK, Sarkar S, Sinha VK (2012): External ear abnormalities in existing scales for minor physical anomalies: are they enough? Psychiatry Res 198:324-6.

Purcell SM, Moran JL, Fromer M, Ruderfer D, Solovieff N, Roussos P, O'Dushlaine C, Chambert K, Bergen SE, Kähler A, Duncan L, Stahl E, Genovese G, Fernández E, Collins MO, Komiyama NH, Choudhary JS, Magnusson PK, Banks E, Shakir K, Garimella K, Fennell T, DePristo M, Grant SG, Haggarty SJ, Gabriel S, Scolnick EM, Lander ES, Hultman CM, Sullivan PF, McCarroll SA, Sklar P (2014): A polygenic burden of rare disruptive mutations in schizophrenia. Nature 506(7487):185-90. .

Rajchgot H, Fathalli F, Rajchgot P, Menezes N, Joober R, Boksa P (2009): Decreased tooth size in schizophrenia. Schizophr Res 110:194-6. Ramanathan S, Miewald J, Montrose D, Keshavan MS (2015): Can age at sexual maturity act as a predictive biomarker for prodromal negative symptoms? Schizophr Res 164:35-9.

Ramsey JM, Schwarz E, Guest PC, van Beveren NJ, Leweke FM, Rothermundt M, Bogerts B, Steiner J, Bahn S (2013): Distinct molecular phenotypes in male and female schizophrenia patients. PLoS One 8:e78729.

Ravasi T, Suzuki H, Cannistraci CV, Katayama S, Bajic VB, Tan K, Akalin A, Schmeier S, Kanamori-Katayama M, Bertin N, Carninci P, Daub CO, Forrest AR, Gough J, Grimmond S, Han JH, Hashimoto T, Hide W, Hofmann O, Kamburov A, Kaur M, Kawaji H, Kubosaki A, Lassmann T, van Nimwegen E, MacPherson CR, Ogawa C, Radovanovic A, Schwartz A, Teasdale RD, Tegnér J, Lenhard B, Teichmann SA, Arakawa T, Ninomiya N, Murakami K, Tagami M, Fukuda S, Imamura K, Kai C, Ishihara R, Kitazume Y, Kawai J, Hume DA, Ideker T, Hayashizaki Y(2010): An atlas of combinatorial transcriptional regulation in mouse and man. Cell 140(5):744-52.

Rehkämper G, Frahm HD, Cnotka J (2008): Mosaic evolution and adaptive brain component alteration under domestication seen on the background of evolutionary theory. Brain Behav Evol 71: 115-26.

Rich AM, Cho YT, Tang Y, Savic A, Krystal JH, Wang F, Xu K, Anticevic A (2016): Amygdala volume is reduced in early course schizophrenia. Psychiatry Res 250:50-60.

Richter R, Rorbach J, Pajak A, Smith PM, Wessels HJ, Huynen MA, Smeitink JA, Lightowlers RN, Chrzanowska-Lightowlers ZM (2010): A functional peptidyl-tRNA hydrolase, ICT1, has been recruited into the human mitochondrial ribosome. EMBO J 29(6):1116-25.

Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kähler AK, Akterin S, Bergen SE, Collins AL, Crowley JJ, Fromer M, Kim Y, Lee SH, Magnusson PK, Sanchez N, Stahl EA, Williams S, Wray NR, Xia K, Bettella F, Borglum AD, Bulik-Sullivan BK, Cormican P, Craddock N, de Leeuw C, Durmishi N, Gill M, Golimbet V, Hamshere ML, Holmans P, Hougaard DM, Kendler KS, Lin K, Morris DW, Mors O, Mortensen PB, Neale BM, O'Neill FA, Owen MJ, Milovancevic MP, Posthuma D, Powell J, Richards AL, Riley BP, Ruderfer D, Rujescu D, Sigurdsson E, Silagadze T, Smit AB, Stefansson H, Steinberg S, Suvisaari J, Tosato S, Verhage M, Walters JT; Multicenter Genetic Studies of Schizophrenia Consortium., Levinson DF, Gejman PV, Kendler KS, Laurent C, Mowry BJ, O'Donovan MC, Owen MJ, Pulver AE, Riley BP, Schwab SG, Wildenauer DB, Dudbridge F, Holmans P, Shi J, Albus M, Alexander M, Campion D, Cohen D, Dikeos D, Duan J, Eichhammer P, Godard S, Hansen M, Lerer FB, Liang KY, Maier W, Mallet J, Nertney DA, Nestadt G, Norton N, O'Neill FA, Papadimitriou GN, Ribble R, Sanders AR, Silverman JM, Walsh D, Williams NM, Wormley B; Psychosis Endophenotypes International Consortium, Arranz MJ, Bakker S, Bender S, Bramon E, Collier D, Crespo-Facorro B, Hall J, Iyegbe C, Jablensky A, Kahn RS, Kalaydjieva L, Lawrie S, Lewis CM, Lin K, Linszen DH, Mata I, McIntosh A, Murray RM, Ophoff RA, Powell J, Rujescu D, Van Os J, Walshe M, Weisbrod M, Wiersma D; Wellcome Trust Case Control Consortium 2., Donnelly P, Barroso I, Blackwell JM, Bramon E, Brown MA, Casas JP, Corvin AP, Deloukas P, Duncanson A,

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Jankowski J, Markus HS, Mathew CG, Palmer CN, Plomin R, Rautanen A, Sawcer SJ, Trembath RC, Viswanathan AC, Wood NW, Spencer CC, Band G, Bellenguez C, Freeman C, Hellenthal G, Giannoulatou E, Pirinen M, Pearson RD, Strange A, Su Z, Vukcevic D, Donnelly P, Langford C, Hunt SE, Edkins S, Gwilliam R, Blackburn H, Bumpstead SJ, Dronov S, Gillman M, Gray E, Hammond N, Jayakumar A, McCann OT, Liddle J, Potter SC, Ravindrarajah R, Ricketts M, Tashakkori-Ghanbaria A, Waller MJ, Weston P, Widaa S, Whittaker P, Barroso I, Deloukas P, Mathew CG, Blackwell JM, Brown MA, Corvin AP, McCarthy MI, Spencer CC, Bramon E, Corvin AP, O'Donovan MC, Stefansson K, Scolnick E, Purcell S, McCarroll SA, Sklar P, Hultman CM, Sullivan PF (2013): Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat Genet 45(10):1150-9.

Romano A, Tempesta B, Micioni Di Bonaventura MV, Gaetani S (2016): From autism to eating disorders and more: the role of oxytocin in neuropsychiatric disorders. Front Neurosci 9:497. Romero T, Nagasawa M, Mogi K, Hasegawa T, Kikusui T (2015): Intranasal administration of oxytocin promotes social play in domestic dogs. Commun Integr Biol 8:e1017157.

Rosa JC, César MC (2016): Role of hexokinase and VDAC in neurological disorders. Curr Mol Pharmacol 9:320-331.

Ruest LB, Hammer RE, Yanagisawa M, Clouthier DE (2003): Dlx5/6-enhancer directed expression of Cre recombinase in the pharyngeal arches and brain. Genesis 37:188-194.

Ruzicka WB, Subburaju S, Benes FM (2015): Circuit- and diagnosis-specific DNA methylation changes at γ-aminobutyric acid-related genes in postmortem human hippocampus in schizophrenia and bipolar disorder. JAMA Psychiatry 72:541-51.

Sajan SA, Rubenstein JL, Warchol ME, Lovett M (2011): Identification of direct downstream targets of Dlx5 during early inner ear development. Hum Mol Genet 20:1262-73.

Sakane F, Miyamoto Y (2013): N-cadherin regulates the proliferation and differentiation of ventral midbrain dopaminergic progenitors. Dev Neurobiol 73: 518-29.

Salmela E, Renvall H, Kujala J, Hakosalo O, Illman M, Vihla M, Leinonen E, Salmelin R, Kere J (2016): Evidence for genetic regulation of the human parieto-occipital 10-Hz rhythmic activity. Eur J Neurosci 44:1963-71.

Sánchez-Villagra MR, Geiger M, Schneider RA (2016): The taming of the neural crest: a developmental perspective on the origins of morphological covariation in domesticated mammals. R Soc Open Sci 3:160107.

Sans-Sansa B, McKenna PJ, Canales-Rodríguez EJ, Ortiz-Gil J, López-Araquistain L, Sarró S, Dueñas RM, Blanch J, Salvador R, Pomarol-Clotet E (2013): Association of formal thought disorder in schizophrenia with structural brain abnormalities in language-related cortical regions. Schizophr Res 146:308-13.

Sasai N, Kutejova E, Briscoe J (2014): Integration of signals along orthogonal axes of the vertebrate neural tube controls progenitor competence and increases cell diversity. PLoS Biol 12(7):e1001907.

Sasayama D, Hattori K, Teraishi T, Hori H, Ota M, Yoshida S, Arima K, Higuchi T, Amano N, Kunugi H (2012): Negative correlation between cerebrospinal fluid oxytocin levels and negative symptoms of male patients with schizophrenia. Schizophr Res 139:201–206. Saugstad LF (1989a): Mental illness and cognition in relation to age at puberty: a hypothesis. Clin Genet 36:156-67.

Saugstad LF (1989b): Age at puberty and mental illness. Towards a neurodevelopmental aetiology of Kraepelin's endogenous psychoses. Br J Psychiatry 155:536-44.

Schneider SA, Marshall KE, Xiao J, LeDoux MS (2012): JPH3 repeat expansions cause a progressive akinetic-rigid syndrome with severe dementia and putaminal rim in a five-generation African-American family. Neurogenetics 13:133-40. Seixas AI, Holmes SE, Takeshima H, Pavlovich A, Sachs N, Pruitt JL, Silveira I, Ross CA, Margolis RL, Rudnicki

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

DD (2012): Loss of junctophilin-3 contributes to Huntington disease-like 2 pathogenesis. Ann Neurol 71:245-57.

Shao L, Vawter MP (2008): Shared gene expression alterations in schizophrenia and bipolar disorder. Biol Psychiatry 64:89-97.

Shoshan-Barmatz V, Ben-Hail D, Admoni L, Krelin Y, Tripathi SS (2015): The mitochondrial voltage-dependent anion channel 1 in tumor cells. Biochim Biophys Acta 1848: 2547-75.

Sims R, Hollingworth P, Moskvina V, Dowzell K, O'Donovan MC, Powell J, Lovestone S, Brayne C, Rubinsztein D, Owen MJ, Williams J, Abraham R (2009): Evidence that variation in the oligodendrocyte lineage transcription factor 2 (OLIG2) gene is associated with psychosis in Alzheimer's disease. Neurosci Lett 461: 54-9.

Sisek-Šprem M, Križaj A, Jukić V, Milošević M, Petrović Z, Herceg M (2015): Testosterone levels and clinical features of schizophrenia with emphasis on negative symptoms and aggression. Nord J Psychiatry 69:102-9.

Srinivasan S, Bettella F, Hassani S, Wang Y, Witoelar A, Schork AJ,, Thompson WK, Collier DA, Desikan RS, Melle I, Dale AM,, Djurovic S, Andreassen OA. (2017): Probing the association between early evolutionary markers and schizophrenia. PLoS One 12:e0169227.

Srinivasan S, Bettella F, Mattingsdal M, Wang Y, Witoelar A, Schork AJ, Thompson WK, Zuber V; Schizophrenia Working Group of the Psychiatric Genomics Consortium, The International Headache Genetics Consortium, Winsvold BS, Zwart JA, Collier DA, Desikan RS, Melle I, Werge T, Dale AM, Djurovic S, Andreassen OA (2016): Genetic markers of human evolution are enriched in schizophrenia. Biol Psychiatry 80:284-92.

St Pourcain B, Cents RA, Whitehouse AJ, Haworth CM, Davis OS, O'Reilly PF, Roulstone S, Wren Y, Ang QW, Velders FP, Evans DM, Kemp JP, Warrington NM, Miller L, Timpson NJ, Ring SM, Verhulst FC, Hofman A, Rivadeneira F, Meaburn EL, Price TS, Dale PS, Pillas D, Yliherva A, Rodriguez A, Golding J, Jaddoe VW, Jarvelin MR, Plomin R, Pennell CE, Tiemeier H, Davey Smith G (2014). Common variation near ROBO2 is associated with expressive vocabulary in infancy. Nat Commun 5:4831.

Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA (2006): Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry 188:510-8.

Stein CM, Schick JH, Gerry Taylor H, Shriberg LD, Millard C, Kundtz-Kluge A, Russo K, Minich N, Hansen A, Freebairn LA, Elston RC, Lewis BA, Iyengar SK (2004): Pleiotropic effects of a chromosome 3 locus on speech-sound disorder and reading. Am J Hum Genet 74:283-97.

Stephane M, Kuskowski M, Gundel J (2014): Abnormal dynamics of language in schizophrenia. Psychiatry Res 216:320-4.

Stephane M, Pellizzer G, Fletcher CR, McClannahan K (2007): Empirical evaluation of language disorder in schizophrenia. J Psychiatry Neurosci 32:250-8.

Strauss GP, Keller WR, Koenig JI, Gold JM, Frost KH, Buchanan RW (2015): Plasma oxytocin levels predict social cue recognition in individuals with schizophrenia. Schizophr Res 62: 47–51. Sun J, Tang Y, Lim KO, Wang J, Tong S, Li H, He B (2014): Abnormal dynamics of EEG oscillations in schizophrenia patients on multiple time scales. IEEE Trans Biomed Eng 61:1756-1764.

Swillen A, Devriendt K, Legius E, Eyskens B, Dumoulin M, Gewillig M (1997): Intelligence and psychosocial adjustment in velocardiofacial syndrome: A study of 37 children and adolescents with 22q11.2 Deletion Syndrome. J Med Genet 34:453-8.

Swillen A, Devriendt K, Legius E, Prinzie P, Vogels A, Ghesquiere P, Fryns JP (1999): The behavioural phenotype in velo-cardio-facial syndrome (VCFS): from infancy to adolescence. Genet Couns 10:79-88.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, Huerta-Cepas J, Simonovic M, Roth A, Santos A, Tsafou K.P, Kuhn M, Bork P, Jensen LJ , von Mering C (2015): STRING v10: protein-protein interaction networks, integrated over the tree of life. Nucleic Acids Res 43:D447-52.

Tabler JM, Rice CP, Liu KJ, Wallingford JB (2016): A novel ciliopathic skull defect arising from excess neural crest. Dev Biol 417: 4-10.

Takahashi T, Okabe S, Broin PÓ, Nishi A,, Ye K, Beckert MV, Izumi T,, Machida A, Kang G, Abe S, Pena JL, Golden A,, Kikusui T, Hiroi N (2016): Structure and function of neonatal social communication in a genetic mouse model of autism. Mol Psychiatry 21:1208-14.

Takahasi M, Okanoya K (2010): Song learning in wild and domesticated strains of white-rumped munia, Lonchura striata, compared by cross-fostering procedures: domestication increases song variability by decreasing strain-specific bias. Ethology 116:396-405.

Tanimoto Y, Veistinen L, Alakurtti K, Takatalo M, Rice DP (2012): Prevention of premature fusion of calvarial suture in GLI-Kruppel family member 3 (Gli3)-deficient mice by removing one allele of Runt-related transcription factor 2 (Runx2). J Biol Chem 287:21429-38.

Teffer K, Semendeferi K (2012): Human prefrontal cortex: evolution, development, and pathology. Prog Brain Res 195:191-218.

Theofanopoulou C. (2016): Implications of oxytocin in human linguistic cognition: from genome to phenome. Front Neurosci 10:271.

Thomas J (2014): Self-domestication and Language Evolution. PhD thesis. Edinburgh, University of Edinburgh.

Trixler M, Tényi T, Csábi G, Szabó R (2001): Minor physical anomalies in schizophrenia and bipolar affective disorder. Schizophr Res 52:195-201.

Tunca Z, Kıvırcık Akdede B, Özerdem A, Alkın T, Polat S, Ceylan D, Bayın M, Cengizçetin Kocuk N, Şimşek S, Resmi H, Akan P (2015): Diverse glial cell line-derived neurotrophic factor (GDNF) support between mania and schizophrenia: a comparative study in four major psychiatric disorders. Eur Psychiatry 30:198-204.

Van Lierde KM, Mortier G, Loeys B, Baudonck N, De Ley S, Marks LA, Van Borsel J (2007): Overall intelligibility, language, articulation, voice and resonance characteristics in a child with Shprintzen-Goldberg syndrome. Int J Pediatr Otorhinolaryngol 71:721-8.

van Os J, Kapur S (2009): Schizophrenia. Lancet 374: 635–45.

van Reeuwijk J, Maugenre S, van den Elzen C, Verrips A, Bertini E, Muntoni F, Merlini L, Scheffer H, Brunner HG, Guicheney P, van Bokhoven H (2006): The expanding phenotype of POMT1 mutations: from Walker-Warburg syndrome to congenital muscular dystrophy, microcephaly, and mental retardation. Hum Mutat 27:453-9.

Vercammen A, Skilleter AJ, Lenroot R, Catts SV, Weickert CS, Weickert TW (2013): Testosterone is inversely related to brain activity during emotional inhibition in schizophrenia. PLoS One 8:e77496.

Vincentz JW, Casasnovas JJ, Barnes RM, Que J, Clouthier DE, Wang J, Firulli AB (2016): Exclusion of Dlx5/6 expression from the distal-most mandibular arches enables BMP-mediated specification of the distal cap. Proc Natl Acad Sci U S A 113: 7563-8.

von Tetzchner S, Fosse P, Elmerskog B (2013): Juvenile neuronal ceroid lipofuscinosis and education. Biochim Biophys Acta 1832:1894-905.

Walker E, Mittal V, Tessner K (2008): Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. Annu Rev Clin Psychol 4:189-216.

Walker EF, Walder DJ, Reynolds F (2001): Developmental changes in cortisol secretion in normal and at-risk youth. Dev Psychopathol 13:721-32.

bioRxiv preprint doi: https://doi.org/10.1101/072751; this version posted February 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.

Wang R, Chen CC, Hara E, Rivas MV, Roulhac PL, Howard JT, Chakraborty M, Audet JN, Jarvis ED (2015): Convergent differential regulation of SLIT-ROBO axon guidance genes in the brains of vocal learners. J Comp Neurol 523:892-906.

Wegman J, Tyborowska A, Hoogman M, Arias Vásquez A, Janzen G (2016): The brain-derived neurotrophic factor Val66Met polymorphism affects encoding of object locations during active navigation. Eur J Neurosci doi: 10.1111/ejn.13416.

Wilkins, AS, Wrangham RW, Fitch WT (2014): The “domestication syndrome” in mammals: A unified explanation based on neural crest cell behavior and genetics. Genetics 197:795-808.

Williams HJ, Norton N, Peirce T, Dwyer S, Williams NM, Moskvina V, Owen MJ, O'Donovan MC (2007): Association analysis of the glial cell line-derived neurotrophic factor (GDNF) gene in schizophrenia. Schizophr Res 97:271-6.

Wilson SL, Wilson JP, Wang C, Wang B, McConnell SK (2012): Primary cilia and Gli3 activity regulate cerebral cortical size. Dev Neurobiol 72: 1196-212.

Wray A, Grace GW (2007): The consequences of talking to strangers: Evolutionary corollaries of socio-cultural influences on linguistic form. Lingua 117:543-578.

Xu T, Stephane M, Parhi KK (2012): Selection of abnormal neural oscillation patterns associated with sentence-level language disorder in schizophrenia. Conf Proc IEEE Eng Med Biol Soc 2012:4923-6.

Xu T, Stephane M, Parhi KK (2013): Multidimensional analysis of the abnormal neural oscillations associated with lexical processing in schizophrenia. Clin EEG Neurosc. 44:135-143.

Yamauchi K, Varadarajan SG, Li JE, Butler SJ (2013): Type Ib BMP receptors mediate the rate of commissural axon extension through inhibition of cofilin activity. Development 140: 333-42.

Yang H, Manya H, Kobayashi K, Jiao H, Fu X, Xiao J, Li X, Wang J, Jiang Y, Toda T, Endo T, Wu X, Xiong H (2016): Analysis of phenotype, enzyme activity and genotype of Chinese patients with POMT1 mutation. J Hum Genet 61:753-9.

Yoshitsugu K, Yamada K, Toyota T, Aoki-Suzuki M, Minabe Y, Nakamura K, Sekine Y, Suzuki K, Takei N, Itokawa M, Mori N, Yoshikawa T (2006): A novel scale including strabismus and 'cuspidal ear' for distinguishing schizophrenia patients from controls using minor physical anomalies. Psychiatry Res 145:249-58.

Yuan A, Li W, Yu T, Zhang C, Wang D, Liu D, Xu Y, Li H, Yu S (2013): SOX10 rs139883 polymorphism is associated with the age of onset in schizophrenia. J Mol Neurosci 50:333-8. Yüksel RN, Altunsoy N, Tikir B, Cingi Külük M, Unal K, Goka S, Aydemir C, Goka E (2014): Correlation between total vitamin D levels and psychotic psychopathology in patients with schizophrenia: therapeutic implications for add-on vitamin D augmentation. Ther Adv Psychopharmacol 4:268-75.

Zeidán-Chuliá F, de Oliveira BH, Casanova MF, Casanova EL, Noda M, Salmina AB, Verkhratsky A (2016): Up-regulation of oligodendrocyte lineage markers in the cerebellum of autistic patients: evidence from network analysis of gene expression. Mol Neurobiol 53:4019-25.

Zhang D, Ighaniyan S, Stathopoulos L, Rollo B, Landman K, Hutson J, Newgreen D (2014): The neural crest: a versatile organ system. Birth Defects Res C Embryo Today 102:275-98.

Zhang XY (2016): BDNF polymorphisms are associated with cognitive performance in schizophrenia patients versus healthy controls. J Clin Psychiatry 77:e1011-8.

Zhou H, Hu S, Matveev R, Yu Q, Li J, Khaitovich P, Jin L, Lachmann M, Stoneking M, Fu Q, Tang K (2015): A chronological atlas of natural selection in the human genome during the past half-million years. BioRxiv doi: http://dx.doi.org/10.1101/018929.