Schizophrenia and human self-domestication: a linguistic approach

Antonio Benítez-Burraco[1] 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

Abstract

Schizophrenia (SZ) is a pervasive neurodevelopmental disorder entailing social and cognitive deficits, including marked problems with language. SZ incidence has always been high and quite stable in human populations, across time and regardless of cultural implications, due to unclear reasons. Also, its complex multifactorial aetiopathogenesis, including genetic and environmental factors, is widely uncertain. 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 linguistic abilities. 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 many SZ candidate genes are found among the genes involved in the "domestication syndrome", but also among genes implicated in language evolution. Finally, we show that selected genes important for the neural crest development exhibit altered expression profiles in the brain of SZ patients, specifically in areas involved in language processing. Based on these observations, we conclude that language dysfunction in 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.

1. Introduction

Schizophrenia (SZ) is a pervasive neurodevelopmental condition entailing different and severe social and cognitive deficits (van Os and Kapur 2009). 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 elements 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). Overall, this suggests that the evolutionary changes occurred in the human lineage after the split from extinct hominins may help clarifying some aspects of SZ. Conversely, delving into the aetiopathogenesis of this condition might help understanding the changes that brought about our human distinctive cognitive phenotype.

In this paper we wish to explore this possibility by focusing on two aspects that we find intimately related: language deficits in SZ and the self-domestication of the human species. Language deficits are a hallmark of the disease. They usually manifest as problems in speech perception (in the form of auditory verbal hallucinations), abnormal speech production (known as formal thought disorder), 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). This abnormal mode of processing language can be specifically drawn back to a distinctive oscillatory profile of the brain during language computation (Murphy and Benítez-Burraco, 2016a).

In our previous work we 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 (Murphy and Benítez-Burraco, 2016a). The evolution of our language-readiness has been linked to changes in several genes involved in brain and skull development occurred after our split from Neanderthals and Denisovans (see Boeckx and Benítez-Burraco, 2014a, 2014b; Benítez-Burraco and Boeckx, 2015 for details). Nonetheless, we expect that our cognitive phenotype was also modelled by changes occurred later, which we have linked to our self-domestication (Benítez-Burraco et al., in press). The idea of human beings as domesticated primates goes 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 niche provides humans with an extended socialization window, enabling 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 trend is supported by several linguistic studies revealing positive correlations between aspects of linguistic complexity and aspects of social complexity (Lupyan and Dale, 2010; Wray and Grace, 2007), or pointing out to the emergent nature of core properties of human languages, resulting from cultural transmission (Benítez-Burraco, 2016).

Several selectionists' accounts of why humans became self-domesticated have been posited over time, ranging from selection against aggression and towards social tolerance, to a subproduct of mate-choices, to adaptation to the human-made environment (Thomas, 2014). In our recent work we have hypothesised that it 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., in press). 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 Wilikins et al (2014) the set of traits observed in domestic mammals, ranging from changes in the craniofacial region, 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 showed that the complex pathophysiology of some human cognitive diseases affecting language can be, at least in part, linked to an abnormal presentation of the "domestication syndrome". Specifically, we 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 "domestic" traits observed in typically-developing (TD) individuals (Benítez-Burraco et al., 2016). Similarly to SZ, ASD is also characterised by language deficits that can be linked to many of the changes occurred during our speciation (see Benítez-Burraco and Murphy, 2016).

Interestingly, SZ and ASD 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 Bradcock, 2008). We have previously shown that SZ and ASD patients process language differently, and exhibit distinctive oscillatory profiles when processing language (Murphy and Benítez-Burraco, 2016b). 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 aetiopathogenesis of SZ, and related language impairment, under an original standpoint.

To this aim, this paper will first provide a general account of the domesticated traits found in SZ patients. Thereafter, the SZ molecular aetiopathogenesis will be discussed, focusing on candidate genes that play a role in both the development and function of the NC and in the evolution of language-readiness. The functional role of these genes will be considered in the light of the differential expression profiles observed in the SZ brain. We will conclude that SZ can be construed as an aberrant ontogenetic itinerary for the human cognition, resulting in part from changes in the expression profile of genes important for the domestication syndrome, partially overlapping with NC-related genes, and for language-readiness.

2. Domestication features in the SZ clinical spectrum

Most of the features observed in the "domestication syndrome" described by Wilkins and colleagues (2014) are found generally exacerbated in SZ individuals (Figure 1).

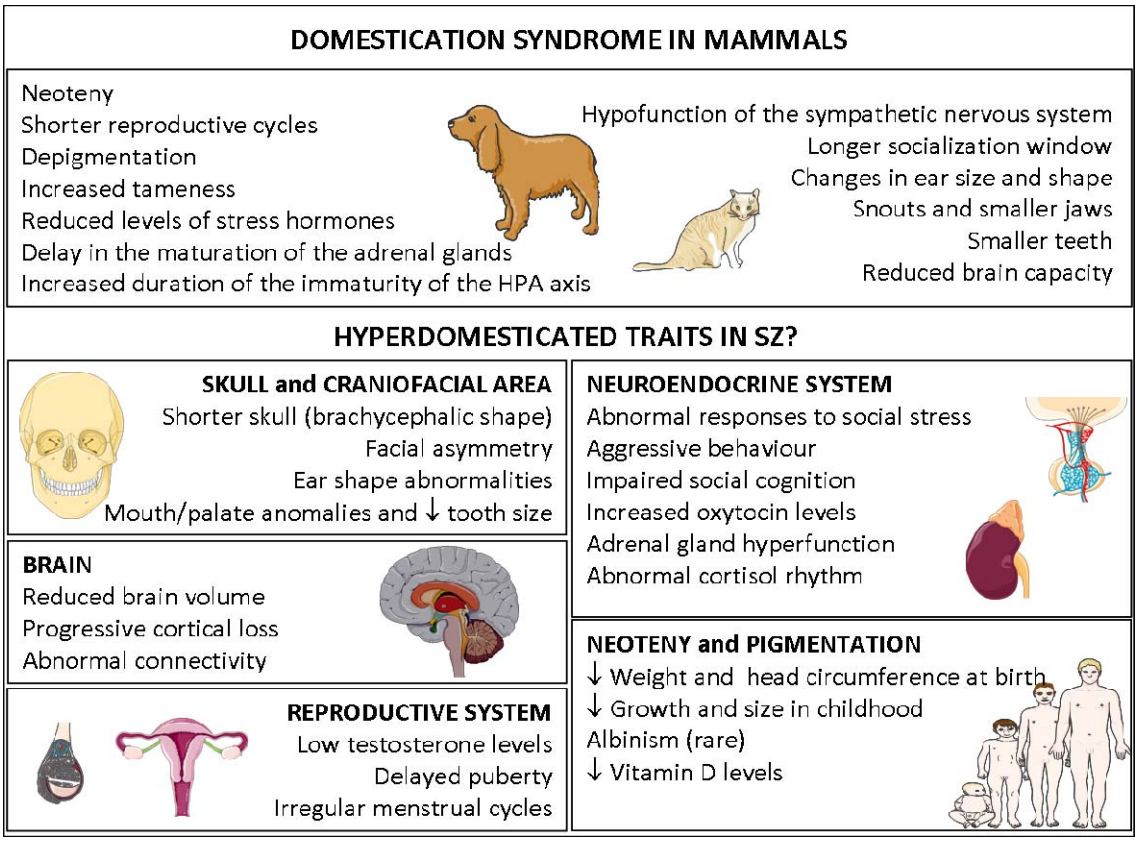


Figure 1. Schizophrenia and the domestication syndrome. The diagram is meant to symbolize the anomalous presentation of the "domestication syndrome" in people with schizophrenia. Main features observed in domesticated mammals (Wilkins et al., 2014; Sánchez-Villlagra, 2016) are shown in the upper box, 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). Some studies suggested a significant association between minor physical anomalies and the early onset of the disease (Hata et al., 2003). 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).

In addition, patients suffering from psychotic disorders tend to feature a more brachycephalic (i.e. shorter) skull (McGrath et al., 2002). Brachycephaly is a frequent skull shape found in domesticated dog and cat breeds (Haworth et al., 2001). In humans, brachycephaly can be due to the premature bilateral fusion of the coronal suture (Lattanzi et al., 2012).

Brain anomalies and dysfunctions

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. Hence brain volume constraint in SZ is 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. Specifically, schizophrenic patients with Formal Thought Disorders (FTDs) 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 patient has 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). 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), but also negative symptoms of the disease (Feifel et al., 2010; Modabbernia et al., 2013; Gibson et al., 2014; Davis et al., 2014).

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 those who are not medicated (Walker et al., 2008). At the same time Hempel et al., (2010) found that cortisol concentration in the plasma of patients decreases more markedly during the day in SZ patients than in healthy controls, and that the decrease of HPA axis sensitivity correlated 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 found that they exhibit a significant absence of the increase in cortisol responsivity to stress (Girshkin et al., 2016). 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. 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). 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 slow growth and small size 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 has 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 individuals 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 controls (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 (namely, 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). 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 aetiopathogenesis 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" might result as the unselected by-product of a reduce input in NC cells (Wilkins et al., 2014). Phenotypes of human neurocristopathies include features that have been described in domesticated mammals (Sánchez-Villagra et al., 2016). Interestingly, well-defined neurocristopathies, namely, velocardiofacial (OMIM#192430) and Di George (OMIM#188400) syndromes, 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. Additionally, we wish note that frontal bone derives from the NC, and coronal sutures represent the boundary between NC- and paraxial mesoderm-derived structures in the skull primordium. Indeed, selected genes involved in both human and animal brachycephalic conditions are related to the NC (Haworth et al., 2001; Lattanzi, 2016). Finally, as we will show in in the next section many SZ candidate genes affect the development and function of the NC. Overall, these disparate lines of evidence suggest that the schizophrenic phenotype might result in part from a dysfunction of the NC and provides additional support to the view of SZ as a "hyperdomesticated" condition.

3. Schizophrenia and the genetics of the "domestication syndrome"

In order to delve into the molecular background of our hypothesis, we first assessed whether genes that are somehow associated to SZ are overrepresented among, or are functionally related to, candidates for domestication (with a particular emphasis on language disabilities). An extended and up-to-date list of SZ-candidate genes has been gathered through literature mining and database search. The list includes genes bearing pathogenic SNPs, genes found mutated in familial forms of the disease, genes resulting from candidate gene approaches and functional studies, and particularly, genes resulting from GWA and CNV/exome sequencing studies. Regarding candidates for domestication, we have implemented an enlarged list of candidates which includes 1. the core set of genes proposed by Wilkins et al (2014); 2. the subset of genes important for the human skull globularization and the emergence of language-readiness that are related to NC development and function (according to Benítez-Burraco et al., in press); and 3. NC-related genes known to play a key role in craniofacial development and related disorders. The reasons for including this third group of genes are that, as noted above, domestication significantly affects the cranial region and that schizophrenics show differences with healthy controls regarding the skull, the face, and the

brain, but also that SZ entails oromotor problems (Rapin et al., 2013; Schiffman et al., 2016). Overall, our selection is based on a candidate gene approach driven by the clinical, somatic, and cognitive features that connect SZ with the "domestication syndrome", widely discussed in previous sections. Table 1 provides the entire list of candidate genes considered in this section.

Gene symbol	Gene name	Domestication[a]	Language-readiness[b]	NCC[c]	Craniofacial[d]	SZ	
						Candidate[e]	Differentially expressed[f]
ALX1	Aristaless-like homeobox protein 1			+	+		
ALX3	Aristaless-like homeobox protein 3			+	+		
ALX4	Aristaless-like homeobox protein 4			+	+		
AXIN2	Axin 2			+	+		+
BAZ1B	Bromodomain adjacent to zinc finger domain 1B	+		+			
BMP2	Bone morphogenetic protein 2		+	+	+		+
BMP7	Bone morphogenetic protein 7		+	+			+
CDC42	Cell division cycle 42		+	+		+	+
CHD7	Chromodomain helicase DNA binding protein 7	+		+			
CITED2	Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 2		+	+			+
CTNNB1	Catenin Beta 1		+	+		+	+
DLX1	Distal-less homeobox 1		+	+		+	+
DLX2	Distal-less homeobox 2		+	+			+
DLX5	Distal-less homeobox 5		+	+	+	+	+
DLX6	Distal-less homeobox 6		+	+	+	+	+
EDN1	Endothelin 1			+	+		+
EDN3	Endothelin 3	+		+			+
EDNRA	Endothelin receptor type A			+	+		+
EDNRB	Endothelin receptor type B	+		+			+
ERF	ETS2 repressor factor			+	+		
FGF7	Fibroblast growth factor 7		+	+			+
FGF8	Fibroblast growth factor 8	+	+	+			+
FGFR1	Fibroblast growth factor receptor 1		+	+	+	+	+
FGFR2	Fibroblast growth factor receptor 2			+	+	+	+
FOXD3	Forkhead box D3	+		+		+	+
FOXP2	Forkhead box P2		+			+	+
FREM1	FRAS1 related extracellular matrix 1			+	+		
GDNF	Glial-derived neurotrophic factor	+		+		+	+
GLI3	GLI family zinc finger 3		+	+	+		+
GRHL3	Grainyhead like transcription factor 3			+	+		
GSC	Goosecoid homeobox			+	+		
HES1	hes family bHLH transcription factor 1		+	+			+
HOXA2	Homeobox A2			+	+		
HSH2D	Hematopoietic SH2 domain containing			+	+		
KIT	KIT proto-oncogene receptor tyrosine kinase	+		+			+

MAGOH	Mago homolog, exon junction complex core component	+		+			
MITF	Microphthalmia-associated transcription factor	+		+			+
MSX1	Msh homeobox 1			+	+	+	+
MSX2	Msh homeobox 2			+	+		
NCAM1	Neural cell adhesion molecule 1		+			+	
NODAL	Nodal growth differentiation factor		+				+
NOG	Noggin			+	+		+
NTN1	Netrin 1			+	+		
PAX3	Paired box 3	+	+	+			+
PAX6	Paired box 6		+	+			+
PAX7	Paired box 7				+		+
POLR1A	Polymerase (RNA) I subunit A				+		+
POU3F2	POU class 3 homeobox 2		+			+	+
PQBP1	Polyglutamine binding protein 1		+				+
PTCH1	Patched 1			+	+		+
RET	Ret proto-oncogene	+		+		+	+
ROBO1	Roundabout guidance receptor 1		+	+		+	
ROBO2	Roundabout guidance receptor 2		+	+		+	+
RUNX2	Runt related transcription factor 2		+	+	+	+	+
SATB2	Special AT-rich sequence binding- homeobox 2		+	+			
SHH	Sonic hedgehog		+	+	+	+	+
SIX2	Sine oculis-related homeobox 2			+	+		+
SLIT1	Slit guidance ligand 1		+	+			+
SLIT2	Slit guidance ligand 2		+	+			+
SOX2	Sex determining region Y-box 2	+	+	+			+
SOX9	Sex determining region Y-box 9	+	+	+	+	+	+
SOX10	Sex determining region Y-box 10	+	+	+		+	
SPECC1L	Sperm antigen with calponin homology and coiled-coil domains 1-like			+	+		
TCF12	Trascription factor 12			+	+		
TCOF1	Treacle ribosome biogenesis factor 1	+		+			
VCAN	Versican		+	+			+
ZIC1	Zinc finger protein family member 1			+	+		+

Table 1. Putative candidate genes for domestication and (language deficits in) schizophrenia.

a. The gene is a candidate for the "domestication syndrome" according to Wilkins et al., (2014). b. The gene is highlighted as a candidate for globularization of the AMH skull/brain and the emergence of language-readiness according to Boeckx and Benítez-Burraco 2014a,b and Benítez-Burraco and Boeckx 2015. c. The gene is involved in neural crest (NC) development and function as resulting from PubMed search. d. The gene is involved in craniofacial development and/or is found mutated in craniofacial syndromes (idem). e. The gene is a candidate for SZ (idem). f. The gene is differentially expressed in post-mortem

brain tissues (cerebellum, temporal cortex, or frontal cortex) of SZ-versus-control individuals (see text for details).

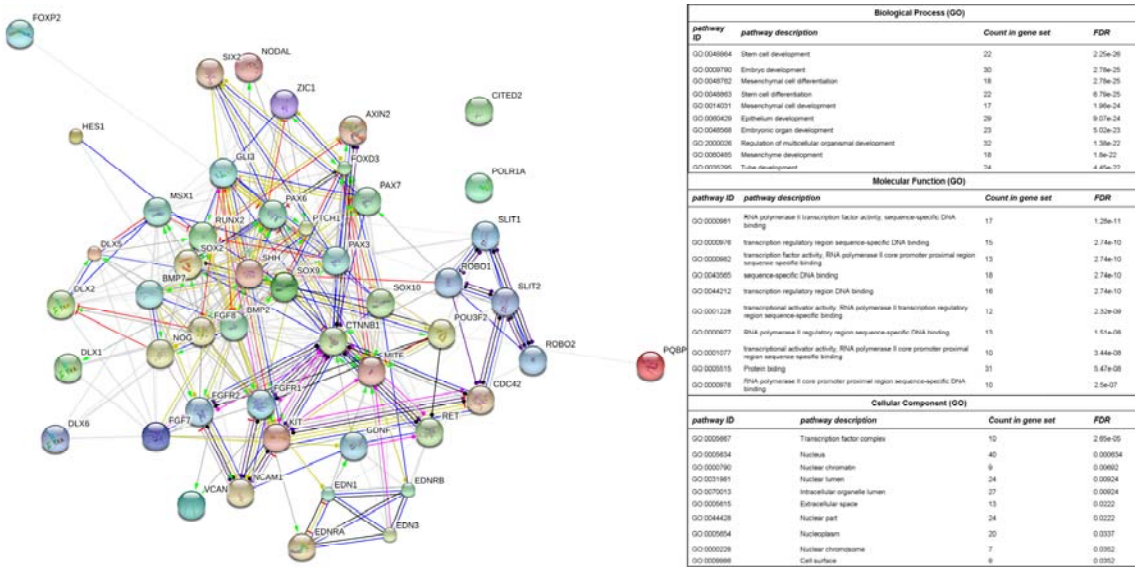
We found out that nearly 30% (20 out of 67) of the genes in the extended list of candidates for domestication (Table 1) have been documented to play some role in the aetiopathogenesis of SZ. This could suggest that SZ-genes are overrepresented among domestication-associated and -related genes, given that only about 5% of human genes have been associated with the disease (1000 out of 20000 protein-coding genes; source: Schizophrenia Gene repository, www.szgene.org).

If our hypothesis is on the right track, we further expected that the genes listed in Table 1 are dysregulated in the brain of SZ patients, particularly in regions that are known to be involved in language processing. Accordingly, we surveyed the Gene Expression Omnibus (GEO) repository (https://www.ncbi.nlm.nih.gov/gds) searching for gene expression datasets obtained from microarray analyses performed in the cerebellum, the temporal cortex, and the frontal cortex of SZ subjects (additional details are provided in Supplemental File 1). We expected that this approach could help identifying new potential candidates for the disease, by providing the proof for genomic loci housing quantitative traits targeting the nervous tissue. Results are summarized in Table 1. Overall, we found significant differential expression values for selected genes, namely:

AXIN2, *CDC42*, *CITED2*, *CTNNB1*, *DLX1*, *DLX5*, *DLX6*, *EDN3*, *FOXP2*, *KIT*, *NOG*, *PQBP1*, and *ROBO2* are downregulated in the striatum of patients with SZ compared to healthy controls, whereas *FGFR1*, *GDNF*, *POLR1A*, *SHH*, and *SOX9* are upregulated in them; *EDN1*, *FOXD3*, *FOXP2*, *MITF*, *ROBO2*, and *SIX2*, are downregulated, while *BMP2*, *DLX2*, *FGF8*, and *VCAN* are upregulated, in the cerebellum of schizophrenics compared with controls; *CTNNB1*, *DLX1*, *HES1*, and *PTCH1* are upregulated, while *EDN1* is downregulated, in the SZ frontal cortex compared with controls; *AXIN2*, *CDC42*, *CITED2*, *CTNNB1*, *EDN3*, *EDNRA*, *FOXD3*, *NOG*, *PAX7*, *POU3F2*, *ROBO2*, *SLIT1*, and *SLIT2* are downregulated in the prefrontal cortex of SZ patients, whereas *BMP7*, *EDNRB*, *FGFR1*, *FGFR2*, *HES1*, *MSX1*, *PAX6*, *RET*, *RUNX2*, *SOX2*, *SOX9*, *VCAN*, and *ZIC1* are upregulated; *FGF7* and *RUNX2* are upregulated, whereas *EDN3* and *PAX3* are downregulated in the temporal cortices of SZ-versus-controls; finally, *BMP7*, *EDN1*, *EDNRB*, *GLI3*, *SOX2*, *SOX9* are upregulated in the temporal cortex of schizophrenics, whereas *EDN3*, *EDNRA*, and *NODAL* are downregulated (Figure 2). Therefore, following this quantitative approach, the number of SZ-related genes sharing functionally overlapping features with the domestications candidates rises nearly 75% (49 out of 67). The detailed biological interpretation and functional profiling of the genes related to SZ within the entire list, is provided in Supplemental file 2.

Figure 2. Expression profiles of candidate genes in the schizophrenic brain. Data were gathered from microarray expression datasets available on the GEO datasets: GSE4036 (Perrone-Bizzozero et al., unpublished) for the cerebellum, GSE53987 (Lanz et al., unpublished) for the striatum, GSE62191 (De Beaumont et al., unpublished) for the frontal cortex, GSE53987 (Lanz et al., unpublished) for the prefrontal cortex, GSE21935 (Barnes et al., 2011) for the temporal cortex, and GSE35977 (Chen et al., 2013) for the parietal cortex. Data are shown as log transformation of fold changes (logFC) between patients and corresponding controls. Only genes showing statistically significant ($p<0.05$) differential expression were considered. Additional details may be found in Supplemental file 1.

We expected that the genes we highlight here as candidates for domestication and SZ (see Table 1) are functionally interconnected and map on to specific signaling cascades, regulatory pathways, or aspects of brain development and function, of interest for SZ aetiopathogenesis and specifically, for language deficits in this condition. Accordingly, String 10 (www.string-db.org) predicted quite robust links between most of these genes (Figure 3). The functional enrichment of the gene list, based on gene ontology (GO) annotations, pointed out that most of the 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 developmental processes of both mesenchymal- and ectodermal-derived structures. Among the molecular function GO categories, transcription regulation hits as the most relevant; indeed many of the genes listed in Table 1 (and discussed in Supplemental File 2) encode transcription factors and epigenetic modulators, that on their turn modulate the expression of genes with pleiotropic role in development and language processing. Finally, considering the cellular localization of the proteins, most of them appear to localize inside the nucleus, within the chromatin, or across the transmembrane region, confirming their role as regulators of transcription and signal transduction.



Biological Process (GO)

pathway ID	pathway description	Count in gene set	FDR
GO:0048864	Stem cell development	22	2.25e-26
GO:0009790	Embryo development	30	2.78e-25
GO:0048762	Mesenchymal cell differentiation	18	2.78e-25
GO:0048863	Stem cell differentiation	22	6.79e-25
GO:0014031	Mesenchymal cell development	17	1.96e-24
GO:0060429	Epithelium development	29	9.07e-24
GO:0048568	Embryonic organ development	23	5.02e-23
GO:2000026	Regulation of multicellular organismal development	32	1.38e-22
GO:0060485	Mesenchyme development	18	1.8e-22
GO:0035295	Tube development	24	4.46e-22

Molecular Function (GO)

pathway ID	pathway description	Count in gene set	FDR
GO:0000981	RNA polymerase II transcription factor activity, sequence-specific DNA binding	17	1.28e-11
GO:0000976	transcription regulatory region sequence-specific DNA binding	15	2.74e-10
GO:0000982	transcription factor activity, RNA polymerase II core promoter proximal region sequence-specific binding	13	2.74e-10
GO:0043565	sequence-specific DNA binding	18	2.74e-10
GO:0044212	transcription regulatory region DNA binding	16	2.74e-10
GO:0001228	transcriptional activator activity, RNA polymerase II transcription regulatory region sequence-specific binding	12	2.32e-09
GO:0000977	RNA polymerase II regulatory region sequence-specific DNA binding	15	1.61e-08
GO:0001077	transcriptional activator activity, RNA polymerase II core promoter proximal region sequence-specific binding	10	3.44e-08
GO:0005515	Protein biding	31	5.47e-08
GO:0000978	RNA polymerase II core promoter proximal region sequence-specific DNA binding	10	2.5e-07

Cellular Component (GO)

pathway ID	pathway description	Count in gene set	FDR
GO:0005667	Transcription factor complex	10	2.65e-05
GO:0005634	Nucleus	40	0.000634
GO:0000790	Nuclear chromatin	9	0.00602
GO:0031981	Nuclear lumen	24	0.00924
GO:0070013	Intracellular organelle lumen	27	0.00924
GO:0005615	Extracellular space	13	0.0222
GO:0044428	Nuclear part	24	0.0222
GO:0005654	Nucleoplasm	20	0.0337
GO:0000228	Nuclear chromosome	7	0.0352
GO:0009986	Cell surface	9	0.0352

Figure 3. Gene interaction network. The diagram shows the network of known and predicted interactions among genes proposed as candidates for domestication and SZ (genes with positive tags in the last two right-sided columns in Table 1). The network was drawn using String (version 10.0; Szklarczyk et al., 2015)) license-free software (http://string-db.org/). 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: posttranslational 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-mention 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 Bonfferoni 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.

4. Schizophrenia and the evolution of human cognition

Different line of evidence supports the view that SZ may be a by-product of the brain changes that resulted in modern cognition. In this paper we have focused on language deficits in SZ, because human cognition boils down to our improved faculty of language (see Boeckx and Benítez-Burraco 2014a for discussion), and because, as noted in section 1, the major positive symptoms of SZ can be reduced to an abnormal linguistic computation (Hinzen and Roselló 2015). As with other features of the disease, language impairment in SZ has been hypothesised to be linked to the evolution of the human faculty for language. Specifically, the mirror system, which has been claimed to provide the evolutionary scaffolding for imitation abilities involved in language acquisition, seems to be dysfunctional in schizophrenics, because they are unable to attribute the generation of an action to themselves (Arbib and Mundhenk 2005). Likewise, Crow (1997, 2008) has claimed that SZ represents an extreme of evolutionary variation of hemispheric specialisation which is also important for speech and language processing. In our previous work we showed that candidates for SZ are overrepresented among the genes believed to be involved in the evolution of our language-readiness (Murphy and Benítez-Burraco 2016a). In this paper we have focused on socialization, a crucial step in the achievement of many cognitive abilities that are a signature of the human condition, particularly language. Specifically, we have considered new accounts of human cognitive evolution that focus on the emergence of the cognitive niche that allowed modern language to develop, which some authors have linked to the self-domestication of the human species.

As we have shown in the paper, to some extent traits related to domestication are found exacerbated in people with SZ. Likewise, genes that are important for domestication and for the evolution of our language readiness are enriched in SZ candidates. And many of them show abnormal expression patterns in the brains of schizophrenics. As we showed in our previous work on this issue, many features of the domesticated phenotype are found attenuated in specular conditions to SZ like ASD, from morphology to physiology to behaviour (see Benítez-Burraco et al., 2016 for details). Likewise, many ASD candidates are also involved in the "domestication syndrome" and in language function: they show altered expression profiles in the brain of autists and some of them exhibit the same expression profile in people with ASD and chimps, and an opposite profile to healthy subjects, in brain areas involved in language processing (Benítez-Burraco et al., 2016).

We have examined the expression profile in the same areas of the chimp brain and the brain of people with ASD of those of our SZ candidates that we have found dysregulated in the brain of schizophrenics. Unfortunately, we couldn't obtain enough significant data from the gene expression datasets and no coherent pattern emerged (results not shown). Nonetheless, if our hypothesis turns to be on the right track and SZ can be really construed as a hyperdomesticated phenotype, we expect that in healthy controls the genes we have

highlighted in this paper show expression patterns that are somehow in-between the patterns found in schizophrenics and in wild primates and in people with ASD.

5. Conclusions

Taken together, the data discussed in this paper may provide original hints towards the clarification of some aspect of SZ aetiopathogenesis, balancing genetic, epigenetic and environmental factors, and merging development and evolution. Specifically, the putative involvement of the NC in the aetiopathogenesis of the disease emerges as a promising avenue for future research on this condition. In addition, the proposed approach may help to disentangle the evolutionary history of the human faculty of language, supporting 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.

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).

References

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. doi: 10.1016/j.psychres.2011.04.023.

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. doi: 10.1186/1471-2148-10-351.

Angrilli A, Spironelli C, Elbert T, Crow TJ, Marano G, Stegagno L. (2009): Schizophrenia as failure of left hemispheric dominance for the phonological component of language. PLoS One. 4:e4507. doi: 10.1371/journal.pone.0004507. Epub 2009 Feb 18.

Arbib MA, Mundhenk TN (2005): Schizophrenia and the mirror system: an essay. Neuropsychologia 43: 268-80.

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. doi: 10.3389/fpsyt.2013.00175.

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.

Beckmann H, Lang RE, Gattaz WF. (1985): Vasopressin–oxytocin in cerebrospinal fluid of schizophrenic patients and normal controls. Psychoneuroendocrinology 10: 187–191. 10.1016/0306-4530(85)90056-3

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 doi: 10.3389/fnins.2016.00373.

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

Benítez-Burraco A, Theofanopoulou C, Boeckx C (in press): Globulartization and domestication. Topoi doi: 10.1007/s11245-016-9399-7

Boeckx C, Benítez-Burraco A (2014a): The shape of the human language-ready brain. Front. Psychol. Front Psychol. 5:282. doi: 10.3389/fpsyg.2014.00282

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. doi: 10.1242/bio.012005.

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. doi: 10.1177/1359786810385491

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

Cannon M, Jones PB, Murray RM (2002): Obstetric complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry159:1080-92.

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. doi: 10.1038/mp.2012.146.

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. doi: 10.1016/j.neubiorev.2014.09.004.

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

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.

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

Crow TJ (1997): Is schizophrenia the price that Homo sapiens pays for language? Schizophr. Res. 28:127-41.

Crow TJ (2008): The 'big bang' theory of the origin of psychosis and the faculty of language. Schizophr. Res. 102:31-52.

Czepielewski LS, Wang L, Gama CS, Barch DM (2016): The relationship of intellectual functioning and cognitive performance to brain structure in schizophrenia. Schizophr Bull Jul 1. pii: sbw090.

Darrell-Berry H, Berry K, Bucci S (2016): The relationship between paranoia and aggression in psychosis: A systematic review. Schizophr Res 172:169-76. doi: 10.1016/j.schres.2016.02.009.

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. 10.1038/npp.2014.68

de Baumont A, Maschietto M, Lima L, Carraro DM, Olivieri EH, Fiorini A, 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. doi:10.1016/j.schres.2014.10.055.

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. doi: 10.1093/schbul/sbv014.

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

Ellis SE, Panitch R, West AB, Arking DE (2016): Transcriptome analysis of cortical tissue reveals shared sets of downregulated genes in autism and schizophrenia. Transl Psychiatry 6:e817. doi: 10.1038/tp.2016.87.

Epstein-Lubow G, Hochstadt J, Lieberman P, Kaplan GB (2006): Speech production in schizophrenia: preliminary data regarding voice onset time. Schizophr Res 82:267-9.

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. doi:10.1242/dev.126573.

Feifel D, Macdonald K, Cobb P, Minassian A (2012): Adjunctive intranasal oxytocin improves verbal memory in people with schizophrenia. Schizophr Res 139: 207–210. doi: 10.1016/j.schres.2012.05.018

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. doi:10.1016/j.biopsych.2010.04.039

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.

Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S (2013): Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci Biobehav Rev 37:1680-91. doi:10.1016/j.neubiorev.2013.06.001.

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. doi:10.1016/j.schres.2014.04.009.

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. doi: 10.1016/j.psyneuen.2016.01.021.

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. doi: 10.1177/0004867415590459.

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.

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. doi: 10.1155/2015/615356.

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.

Gulsuner S, Walsh T, Watts AC, Lee MK, Thornton AM, Casadei S, Rippey C, Shahin H; Consortium on the Genetics of Schizophrenia (COGS), PAARTNERS Study Group, Nimgaonkar VL, Go RC, Savage RM, Swerdlow NR, Gur RE, Braff DL, King MC, McClellan JM (2013): Spatial and temporal mapping of de novo mutations in schizophrenia to a fetal prefrontal cortical network. Cell 154:518-29.

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.

Gutiérrez-Galve L, Chu EM, Leeson VC, Price G, Barnes TR, Joyce EM, Ron MA (2015): A longitudinal study of cortical changes and their cognitive correlates in patients followed up after first-episode psychosis. Psychol Med. 45:205-16. doi: 10.1017/S0033291714001433.

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. doi: 10.1093/schbul/sbs118.

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. doi: 10.1016/j.psychres.2016.01.036.

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.

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. doi:10.4045/tidsskr.12.1084.

Havelka D, Prikrylova-Kucerova H, Prikryl R, Ceskova E (2016): Cognitive impairment and cortisol levels in first-episode schizophrenia patients. Stress 19:383-9. doi: 10.1080/10253890.2016.1193146.

Haworth KE, Islam I, Breen M, Putt W, Makrinou E, Binns M, Hopkinson D, Edwards Y (2001): Canine TCOF1; cloning, chromosome assignment and genetic analysis in dogs with different head types. Mamm Genome 12:622-9.

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. doi: 10.1111/j.1440-1819.2010.02121.x.

Hershey CL, Fisher DE (2005): Genomic analysis of the Microphthalmia locus and identification of the MITF-J/Mitf-J isoform. Gene 347:73–82.

Hinzen W, Rosselló J (2015): The linguistics of schizophrenia: thought disturbance as language pathology across positive symptoms. Front Psychol 6: 971. doi:10.3389/fpsyg.2015.00971.

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

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. doi:10.1016/j.schres.2016.02.005.

Jansen LM, Gispen-de Wied CC, Wiegant VM, Westenberg HG, Lahuis BE, van Engeland H (2006): Autonomic and neuroendocrine responses to a psychosocial stressor in adults with autistic spectrum disorder. J Autism Dev Disord 36:891–899. doi:10.1007/s10803-006-0124-z

Joksimovic M, Anderegg A, Roy A, Campochiaro L, Yun B, Kittappa R, McKay R, Awatramani R (2009): Spatiotemporally separable Shh domains in the midbrain define distinct dopaminergic progenitor pools. Proc Natl Acad Sci U S A.106:19185-90. doi: 10.1073/pnas.0904285106.

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.

Komori T (2011): Signaling networks in RUNX2-dependent bone development. J Cell Biochem 112:750-5.

Kosaka H, Munesue T, Ishitobi M, Asano M, Omori M, Sato M, et al (2012): Long-term oxytocin administration improves social behaviors in a girl with autistic disorder BMC Psychiatry 12:110 doi:101186/1471-244X-12-110

Krebs LT, Iwai N, Nonaka S, Welsh IC, Lan Y, Jiang R et al (2003) Notch signaling regulates left-right asymmetry determination by inducing Nodal expression. Genes Dev 17:1207-12

Lang D, Epstein JA (2003): Sox10 and Pax3 physically interact to mediate activation of a conserved c-RET enhancer. Hum Mol Genet 12:937-45.

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, Bukvic N, Barba M, Tamburrini G, Bernardini C, Michetti F, Di Rocco C. (2012) Genetic basis of single-suture synostoses: genes, chromosomes and clinical implications. Child's Nervous System 28 (9): 1301–1310.

Lattanzi, Wanda (2016) Molecular Genetics of Craniosynostosis. eLS. John Wiley & Sons, Ltd: Chichester. doi: 10.1002/9780470015902.a0025186

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. doi: 10.1016/j.schres.2015.08.001.

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.

Liberg B, Rahm C, Panayiotou A, Pantelis C (2016): Brain change trajectories that differentiate the major psychoses. Eur J Clin Invest 46:658-74. doi:10.1111/eci.12641.

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. doi: 10.1016/j.psychres.2012.07.022.

Lord C, Rutter M, Le Couteur A (1994): Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24: 659–685. doi:10.1007/BF02172145

Lowe LA, Supp DM, Sampath K, Yokoyama T, Wright CV, Potter SS, Overbeek P, Kuehn MR. (1996): Conserved left-right asymmetry of nodal expression and alterations in murine situs inversus. Nature 381:158-161.

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

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.

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, et al (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. doi:10.1007/s40263-012-0022-1

Modahl C, Green L, Fein D, Morris M, Waterhouse L, Feinstein C, Levin H (1998): Plasma oxytocin levels in autistic children. Biol. Psychiatry 43: 270–277. doi:10.1016/S0006-3223(97)00439-3

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. doi: 10.1002/ajmg.a.33381.

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. doi: 10.1016/j.psyneuen.2013.02.007.

Mor E, Kano S, Colantuoni C, Sawa A, Navon R, Shomron N (2013): MicroRNA-382 expression is elevated in the olfactory neuroepithelium of schizophrenia patients. Neurobiol Dis 55:1-10. doi: 10.1016/j.nbd.2013.03.011

Murphy E (2015): The brain dynamics of linguistic computation. Front. Psychol. 6:1515. doi: 10.3389/fpsyg.2015.01515.

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. doi: 10.1016/j.neubiorev.2016.07.029.

Niitsu T, Shirayama Y, Matsuzawa D, Shimizu E, Hashimoto K, Iyo M (2014): Association between serum levels of glial cell-line derived neurotrophic factor and attention deficits in schizophrenia. Neurosci Lett 575:37-41. doi: 10.1016/j.neulet.2014.05.034.

Nordholm D, Krogh J, Mondelli V, Dazzan P, Pariante C, Nordentoft M (2013): Pituitary gland volume in patients with schizophrenia, subjects at ultra high-risk of developing psychosis and healthy controls: a systematic review and meta-analysis. Psychoneuroendocrinology 38:2394-404. doi:10.1016/j.psyneuen.2013.06.030

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 provides evidence for association between schizophrenia and a SNP flanking fibroblast growth factor receptor 2. Mol Psychiatry 14:30-6. doi: 10.1038/mp.2008.108.

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 doi: 10.1038/mp.2015.209.

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.

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. doi: 10.1016/j.schres.2011.03.020.

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

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

Radeloff D, Ciaramidaro A, Siniatchkin M, Hainz D, Schlitt S, Weber B, Poustka F, Bölte S, Walter H, Freitag CM (2014): Structural alterations of the social brain: a comparison between schizophrenia and autism. PLoS One 9:e106539. doi:10.1371/journal.pone.0106539.

Rajchgot H, Fathalli F, Rajchgot P, Menezes N, Joober R, Boksa P (2009): Decreased tooth size in schizophrenia. Schizophr Res. 110:194-6. doi: 10.1016/j.schres.2009.02.014.

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. doi: 10.1016/j.schres.2015.02.019.

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. doi:10.1371/journal.pone.0078729.

Rapin L, Dohen M, Polosan M, Perrier P, Lœvenbruck H (2013): An EMG study of the lip muscles during covert auditory verbal hallucinations in schizophrenia. J Speech Lang Hear Res 56:S1882-93. doi: 10.1044/1092-4388(2013/12-0210).

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. doi: 10.1016/j.pscychresns.2016.02.006.

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. doi: 10.3389/fnins.2015.00497.

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. doi: 10.1001/jamapsychiatry.2015.49.

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.

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. 10.1016/j.schres.2012.06.016

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.

Schiffman J, Mittal V, Kline E, Mortensen EL, Michelsen N, Ekstrøm M, Millman ZB, Mednick SA, Sørensen HJ (2015): Childhood dyspraxia predicts adult-onset nonaffective-psychosis-spectrum disorder. Dev Psychopathol 27:1323-30. doi: 10.1017/S0954579414001436.

Shao L, Vawter MP (2008): Shared gene expression alterations in schizophrenia and bipolar disorder. Biol Psychiatry 64:89-97. doi: 10.1016/j.biopsych.2007.11.010.

Shirayama Y, Hashimoto K, Suzuki Y, Higuchi T (2002): Correlation of plasma neurosteroid levels to the severity of negative symptoms in male patients with schizophrenia. Schizophr Res 58:69-74.

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. doi: 10.3109/08039488.2014.947320.

Souza RP, Romano-Silva MA, Lieberman JA, Meltzer HY, MacNeil LT, Culotti JG, Kennedy JL, Wong AH (2010): Genetic association of the GDNF alpha-receptor genes with schizophrenia and clozapine response. J Psychiatr Res 44:700-6. doi: 10.1016/j.jpsychires.2010.01.002.

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

Stachowiak MK, Kucinski A, Curl R, Syposs C, Yang Y, Narla S, Terranova C, Prokop D, Klejbor I, Bencherif M, Birkaya B, Corso T, Parikh A, Tzanakakis ES, Wersinger S, Stachowiak EK (2013): Schizophrenia: a neurodevelopmental disorder-integrative genomic hypothesis and therapeutic implications from a transgenic mouse model. Schizophr Res 143:367-76. doi: 10.1016/j.schres.2012.11.004.

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.

Stephane M, Kuskowski M, Gundel J (2014): Abnormal dynamics of language in schizophrenia. Psychiatry Res 216:320-4. doi: 10.1016/j.psychres.2014.02.027.

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. doi:10.1016/j.schres.2015.01.034

Suga M, Uetsuki M, Takizawa R, Araki T, Kasai K (2011): Phonological fluency is uniquely impaired in Japanese-speaking schizophrenia patients: confirmation study. Psychiatry Clin Neurosci 65:672-5. doi: 10.1111/j.1440-1819.2011.02281.x.

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. doi: 10.1093/nar/gku1003.

Tachibana M, Kagitani-Shimono K, Mohri I, Yamamoto T, Sanefuji W, Nakamura A, Oishi M, Kimura T, Onaka T, Ozono K, Taniike M (2013): Long-term administration of intranasal oxytocin is a safe and promising therapy for early adolescent boys with autism spectrum disorders. J Child Adolesc Psychopharmacol 23:123–127. 10.1089/cap.2012.0048

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.

Tassabehji M, Newton VE, Read AP (1994): Waardenburg syndrome type 2 caused by mutations in the human microphthalmia (MITF) gene. Nature Genetics 8:251–255.

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

Terpstra J, Gispen-De Wied CC, Broekhoven MH, Frankhuijzen AC, Kahn RS, van Ree JM, Wiegant VM (2003): Attenuated stress responsiveness in an animal model for neurodevelopmental psychopathological disorders. Eur Neuropsychopharmacol 13:249-56.

Terwisscha van Scheltinga AF, Bakker SC, Kahn RS, Kas MJ (2013): Fibroblast growth factors in neurodevelopment and psychopathology. Neuroscientist 19:479-94. doi: 10.1177/1073858412472399

Theofanopoulou C. (2016): Implications of oxytocin in human linguistic cognition: from genome to phenome. Front Neurosci 10:271. doi: 10.3389/fnins.2016.00271.

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. doi: 10.1016/j.eurpsy.2014.11.003.

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

Veijola J, Guo JY, Moilanen JS, Jääskeläinen E, Miettunen J, Kyllönen M, Haapea M, Huhtaniska S, Alaräisänen A, Mäki P, Kiviniemi V, Nikkinen J, Starck T, Remes JJ, Tanskanen P, Tervonen O, Wink AM, Kehagia A, Suckling J, Kobayashi H, Barnett JH, Barnes A, Koponen HJ, Jones PB, Isohanni M, Murray GK (2014): Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition and antipsychotic medication. PLoS One 9:e101689. doi:10.1371/journal.pone.0101689.

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. doi: 10.1371/journal.pone.0077496.

Volk DW, Edelson JR, Lewis DA (2016): Altered expression of developmental regulators of parvalbumin and somatostatin neurons in the prefrontal cortex in schizophrenia. Schizophr Res pii: S0920-9964(16)30094-9. doi:10.1016/j.schres.2016.03.001.

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.

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.

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

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. doi: 10.1007/s12031-013-9982-y.

Yuan A, Yi Z, Sun J, Du Y, Yu T, Zhang C, Liu Y, Zhou Y, Liu D, Li H, Xu Y, Cheng Z, Li W, Yu S (2012): Effect of SOX10 gene polymorphism on early onset schizophrenia in Chinese Han population. Neurosci Lett 521:93-7. doi: 10.1016/j.neulet.2012.05.040.

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. doi:10.1177/2045125314553612.

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. doi: 10.1002/bdrc.21081.