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Transcription Factors in Neurodevelopmental and Associated Psychiatric Disorders: A Potential Convergence for Genetic and Environmental Risk Factors

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Abstract

Neurodevelopmental disorders (NDDs) are a heterogeneous and highly prevalent group of psychiatric conditions marked by impairments in the nervous system. Their onset occurs during gestation, and the alterations are observed throughout the postnatal life. Although many genetic and environmental risk factors have been described in this context, the interactions between them challenge the understanding of the pathways associated with NDDs. Transcription factors (TFs) – a group of over 1,600 proteins that can interact with DNA, regulating gene expression through modulation of RNA synthesis, represent a point of convergence for different risk factors. In addition, TFs organize critical processes like angiogenesis, blood-brain barrier formation, myelination, neuronal migration, immune activation, and many others in a time and location-dependent way. In this review, we summarize important TF alterations in NDD and associated disorders, along with specific impairments observed in animal models, and, finally, establish hypotheses to explain how these proteins may be critical mediators in the context of genome-environment interactions.
Key Words: Transcription Factors; Neurodevelopmental Disorders; Psychiatric Disorders; Environment-Genome Interaction; Transcription; Animal Model.

1. Introduction

Throughout development, both genetic and environmental risk factors contribute to the onset of neural disorders. The genetic risk factor is widely acknowledged, and many genes triggering these conditions are well-described. However, the contribution of environmental risk factors to the onset of neurodevelopmental disorders (NDDs) still poses a great challenge for science since a wide range of alterations in biological pathways can lead to similar outcomes. Recently, many studies have indicated that transcription factors (TFs) could be a point of convergence to understand these interactions.

NDDs are a diverse group of early-onset conditions characterized by impairments in language, cognition, motricity, and many other aspects. This group includes specific learning disorders, motor disorders, and communication disorders, attention deficit hyperactivity disorder (ADHD), intellectual disabilities (ID) and autism spectrum disorder (ASD) (American Psychiatric Association, 2013) (Figure 1). In this context, we reviewed the NDDs with a solid and well-established association with imbalance in the levels/ function of TFs. Specific learning disorders, motor disorders, communication disorders, and ADHD have few descriptions in the literature regarding changes in TFs throughout neurodevelopment; therefore, they were not considered in the study.

ASD is one of the most increasingly prevalent NDD, with a rate of 1:54 among children up to 8 years of age in the USA (Maenner et al., 2020) being characterized by a dyad of behavioral characteristics: 1. deficits in communication and social interaction, and 2. presence of repetitive and stereotyped behaviors, in addition to restricted interest in activities. Recent genetic studies indicate an overlap of symptoms and pathogenic mechanisms among NDDs (like ASD and ID) and other psychiatric disorders, such as schizophrenia (Morris-Rosendahl and Crocq, 2020).

Schizophrenia is characterized by positive symptoms (hallucinations or delusions) and negative symptoms (such as poverty of speech and impairments in cognition). It is estimated to affect about 1.5 per 10,000 people (McGrath et al., 2008), with symptoms typically starting in early adulthood, around 20 years of age (Association, 2013). Therefore, considering the emerging evidence of overlap with ASD symptoms, schizophrenia was included in the study (Figure 1).

In the present review, we described: 1. General features of TFs in NDDs, providing an overview of their expression patterns; 2. NDDs associated with specific

genetic alterations in TFs, including Rett syndrome, Williams syndrome, and Pitt-Hopkins syndrome; 3. The correlation of environmental factors with alterations in TFs; 4. The changes in TFs in multifactorial disorders - focusing on ASD and Schizophrenia - demonstrating that genetic and environmental risk factors can propagate similar alterations; 5. TFs that are not strictly associated with specific disorders but seem to impact important aspects of NDDs in general, like language development; and 6. Integrative perspectives regarding TFs and NDDs.

1.1 An Overview about Transcription Factors

TFs are proteins with DNA-binding properties that orchestrate the transcriptional machinery, regulating rate, time, location, and several other conditions involved in gene expression. The specific transcriptome from each cell type is governed by a particular set of TFs, which defines cellular identities and programming (Cevallos et al., 2020).

Besides the DNA-binding sites, TFs can contain ligand-binding sites, protein-protein interaction sites, and enzymatic activity domains (Lambert et al., 2018). These features are grouped as effector domains since they actively mediate the functions of the TFs, enabling them to perform several actions such as responding to stimuli, dimerization, regulation of RNA-polymerases functions, and modulation of DNA access by indirect interference on histone modifications (Xin and Rohs, 2018). In humans, over 1,600 TFs have already been described (Lambert et al., 2018), grouped into classes by similarities in the DNA-binding domains. Approximately 90% of the TFs in humans are included in one of the three major classes: Basic Domain, Zinc Coordinating Domain, and Helix-turn-helix Domain (Wingender et al., 2015).

The several contributions of TFs in fundamental biological pathways (like cell cycle, neurodevelopment, and immune activation, for example) highlight the importance of time, location, and context throughout biological development. In *Drosophila* studies, this issue is demonstrated by *Hox* (Homeobox) TFs (which regulates the structure of body plan), since alterations in the transcription of *Hox* along body segments generate abrupt abnormalities like ectopic growth of legs (Kaufman et al., 1980) or duplicated thorax (Weatherbee et al., 1998). In humans, extreme alterations like the described in *Drosophila* are probably incompatible with life; nonetheless, subtle alterations may lead to important impacts - mutations in *TP53* (tumor protein p53), for example, can induce major deregulation of the cell cycle,

resulting in tumor growth (Blagih et al., 2020). Similarly, several single nucleotide polymorphisms (SNP) in TFs were already related to psychiatric disorders (Pearl et al., 2019).

All of the TFs addressed in this review are summarized in Table 1, with information regarding their main DNA-binding domains and the regions or specific cell types where these TFs present higher expression in embryonic tissue (focusing on the nervous system and immune system). In Figure 2, the peak of expression of each TF was demonstrated in the two regions that presented complete information regarding the time course of expression: forebrain and cerebellum. All information was obtained from LifeMap Discovery™ (Edgar et al., 2013) and "Evo-devo mammalian app" (Cardoso-Moreira et al., 2019).

2. Genetic-associated neurodevelopmental disorders

This section discusses the association among NDDs and specific genetic alterations in TFs (mutations, deletions, and other disturbances), focusing on the mechanisms linking TFs and pathophysiology pathways.

2.1 Rett syndrome

Rett syndrome (RTT), the second leading cause of female intellectual disability, is a progressive NDD, affecting one in 10,000 females (Rosenberg and Pascual, 2014). In most cases, RTT is caused by mutations in the *MECP2* gene (methyl-CpG binding protein 2) (Shahbazian and Zoghbi, 2001), and, in a smaller proportion, in the *FOXG1* gene (forkhead box G1 protein), both described as TFs (Ma et al., 2016).

The protein MeCP2 mostly represses gene expression by modifying chromatin access (Ip et al., 2018). Mutations in this gene notoriously impact neurodevelopment (Gonzales and LaSalle, 2010), skeletal muscle growth (Conti et al., 2015), liver metabolism (Kyle et al., 2016), heart function (Wang et al., 2018), and other organs. Males with mutations in MECP2 are often stillborn or do not live past infancy, explaining the higher prevalence in females (Weaving et al., 2005).

Animal models of *Mecp2* deletion or haploinsufficiency improved the understanding of possible outcomes resulting from the loss of this protein activity. Mecp2-deficient mice exhibited altered content of GABA and glutamate (in different brain regions in postnatal life) (El-Khoury et al., 2014) and also their receptors (in the CA3 region of the hippocampus) (Calfa et al., 2015), in addition to the loss of the

characteristic barrel field organization in the somatosensory cortex (Lee et al., 2017). The presence of sensory impairments was also observed in zebrafish lacking *mecp2*, probably related to SEMA5B (semaphorin 5B) and ROBO2 (roundabout guidance receptor 2) downregulated expression since these proteins are essential to neuron migration and cortex formation (Leong et al., 2015).

These data emphasize the contribution of MeCP2 in the maintenance of the excitatory/inhibitory balance and the typical organization of the central nervous system (CNS). In this context, deletion of *Mecp2* in mice disrupted the perineuronal net associated with parvalbumin-positive neurons (PV+), inducing enhancement of thalamocortical excitatory inputs to PV+ and, consequently, increasing the inhibitory activity of these cells, which may be related to the “cortex silencing” feature described in RTT patients (Sigal et al., 2019). Silencing or deletion of Mecp2 impaired long-term memory and learning in the hippocampus due to alterations in chromatin organization of CA1 neurons (Gulmez Karaca et al., 2018) and reduced neuronal connectivity between dentate gyrus and entorhinal cortex (Sun et al., 2019). Moreover, mitochondrial-oxygen consumption is enhanced in hippocampal neurons from *Mecp2*-deficient mice, increasing reactive oxygen species (ROS) and probably impairing the functions of these cells (Can et al., 2019).

Glial cells were also observed to be involved in these models. Astrocytes containing *Mecp2* mutations showed decreased expression of the TF Nr2f2 (nuclear receptor subfamily 2 group F member), besides other relevant genes associated with glutamate metabolism and ion transporters, such as lipocalin-2 and chromogranin B (Delépine et al., 2015). Interestingly, astrocytes derived from RTT patients cannot support neuronal development in co-culture (Williams et al., 2014) since disruptions in MeCP2 decrease the expression of EAAT1/2 glutamate transporters and increase the expression of glutamine synthetase, triggering glutamatergic excitotoxicity (Jin et al., 2017). Microglia derived from *Mecp2*-null mice displayed decreased synaptic pruning ability (Schafer et al., 2016), and metabolic alterations regarding glutamate uptake and ROS generation (Jin et al., 2015).

In oligodendrocytes, the total absence of MeCP2, or even its knockdown, induces alterations in cellular morphology, physiology, and survival (Lipi et al., 2018), and increases several myelin genes, like myelin basic protein (*Mbp*), proteolipid protein (*Plp*), myelin oligodendrocyte glycoprotein (*Mog*), and myelin-associated

oligodendrocyte basic protein (*Mobp*) (Sharma et al., 2015), suggesting an important role of MeCP2 in myelination processes.

The serotonergic system is also affected by Mecp2 knockout: a 75-fold increased expression of the serotonin receptor 5b (5-ht5b) was observed in the brainstem of Mecp2−/y mice, and this alteration disrupted the expected downregulation of this receptor in the following steps of neurodevelopment (Vogelgesang et al., 2017). Interestingly, Mecp2-deficient mice also presented alterations in breathing phenotype patterns, which is affected by the 5-ht5b expression (Vogelgesang et al., 2018), emphasizing the relation between serotonin system impairments and MeCP2.

The mutation in the *FOXG1* gene induces severe intellectual, motor, and language disabilities (Ma et al., 2016). Mice with *Foxg1* haploinsufficiency demonstrated enhanced expression of inhibitory synaptic markers (glutamate decarboxylase 67 (GAD67) and GABA AR-α1) and reduced excitatory synaptic markers (VGLUT1, GluA1, GluN1, and PSD-95) in cell culture and mice embryo. In adults, all markers were reduced, indicating a time-dependent action of FOXG1 throughout synaptic neurodevelopment (Patriarchi et al., 2016). Beyond that, an electrophysiological analysis showed cortical hyperexcitability with increased expression of VGLUT and reduced expression of KCC2, indicating a contribution of FOXG1 in the excitatory/inhibitory balance (Wong et al., 2019).

2.2. Pitt-Hopkins syndrome

Pitt–Hopkins syndrome (PTHS) is a condition marked by ID, psychomotor delay, and, in many cases, ASD features (Goodspeed et al., 2018). Despite being first described in 1978 (Pitt and Hopkins, 1978), the cause of PTHS was only elucidated in 2007 (Amiel et al., 2007; Brockschmidt et al., 2007; Zweier et al., 2007): specific mutations in *TCF4* (transcription factor 4). This member of the basic helix-loop-helix TF family (bHLH) regulates gene expression by forming homodimers and heterodimers that can play different roles depending on their dimerization partners (Jones, 2004). Several TFs can dimerize with TCF4 in the brain, such as ATHO1/MATH1 (atonal homolog 1), ASH1/ASCL1 (achaete-scute homolog 1), and NEUROD1 (neuronal differentiation 1) (Navarrete et al., 2013). The brain expression of TCF4 seems to be evolutionarily conserved in humans, rhesus monkeys, and mice. *Tcf4* haploinsufficiency in mice, for example, replicated anomalies found in PTHS

patients, especially in the regulation of neuronal migration (Jung et al., 2018). Furthermore, the specific knockout of *Tcf4* in the CNS of mice induced whole hippocampal architecture impairments and, in the cortex, delayed neural progenitor differentiation and resulted in neuronal morphology alterations in later stages of development (Schoof et al., 2020).

Recently, these hippocampal disturbances were associated with altered neural migration caused by a disruption in radial glia fibers, possibly mediated by WNT pathway protein wnt7b (Wang et al., 2020). Finally, four different mouse models of PTHS highlighted the link between the deficits in the hippocampus-related behaviors and the exaggerated long-term potentiation (LTP) due to increased activation of NMDA receptors in this region (Thaxton et al., 2018).

2.3 Other Genetic Disorders

The SOX (SRY-related HMG-box) proteins have a fundamental role in the developmental regulation (Pillai-Kastoori et al., 2015). Although already described as altered in several disorders, some critical alterations in *SOX* genes result in distinct conditions categorized as separated syndromes. For example, mutations in *SOX5* are related to Lamb-Shaffer syndrome, characterized by ID and speech delay (Lamb et al., 2012); mutations in *SOX10* are associated with Waardenburg–Hirschprung disease, which is marked by neurosensory deafness (Pingault et al., 1998), and, finally, *SOX9* mutations are related to campomelic dysplasia, also associated with hearing loss (Kwok et al., 1995).

Williams syndrome (WS) is a disorder characterized by mild ID and specific cognitive profiles caused by deletions in 7q11.23, a region that includes the *GTF2i* and *GTF2ird* (general transcription factor) genes (Morris, 2017). In mice, knockout of *Gtf2ird* induced alterations in other important TFs associated with neurodevelopment, like *Hey1* (Hes related family BHLH transcription factor with YRPW motif 1), *Myf6* (myogenic factor 6), *Myog* (myogenin), *Dlx2* (distal-less homeobox 2), *Lhx2* (LIM homeobox 2), *Pou3f3* (POU class 3 homeobox 3), *Sox2*, and *Foxp3* (forkhead box protein P3) (Corley et al., 2016). Either partial or total loss of GTF2ird in mice impaired serotonin signaling in the prefrontal cortex. Neurons from layer V of this region demonstrated significantly larger inhibitory outward currents in response to serotonin, which may be associated with the reduced basal anxiety and increased sociability observed in WS individuals (Proulx et al., 2010). Finally, selective deletion of *Gtf2i* in

excitatory forebrain neurons resulted in clinical features of WS and significant impairments in myelination – intervention with a remyelinating drug rescued both oligodendrocytes and behavioral impairments (Barak et al., 2019).

Coffin-Siris syndrome (CSS) is a NDD characterized by ID, facial dysmorphology, microcephaly, and feeding difficulties (Iwamoto et al., 2003). Deletions involving *SOX11* TF were associated with microcephaly, developmental delay, and shared dysmorphic features with CSS. Beyond that, knockdown of *Sox11* in *Xenopus morphants* resulted in diminished head size, confirming this intriguing relation between *SOX11* and microcephaly (Kosho et al., 2014). Interestingly, it was demonstrated that the zika virus infection of SH-SY5Y neuroblastoma cell line induced important up-regulation of miR (145 and 148a) that target *Sox11*, adding evidence to the role of SOX11 in microcephaly (Castro et al., 2019).

Dravet syndrome (DS) is a severe type of refractory epilepsy with early life symptoms. The syndrome is characterized by age-related progression of seizures, cognitive decline, and movement disorders (Akiyama et al., 2010). About 80% of the DS cases are caused by a *de novo* mutation in the sodium voltage-gated channel alpha subunit 1 (*SCN1A*) gene, resulting in Nav1.1 haploinsufficiency (Chopra and Isom, 2014). Human transcriptome analysis demonstrated specific dysregulations of genes associated with chromatin structure, mitotic progression, neural plasticity, and excitability in GABAergic neurons derived from patients, with up-regulation of the TFs FOXM1 and E2F (Transcription Factor E2F1), important regulators of histone modifications and cell cycle (Schuster et al., 2019).

The compilation of all TFs described in the “Genetic-associated neurodevelopmental disorders” section was submitted to Reactome® analysis (Wu and Haw, 2017), resulting in a demonstration of enriched biological pathways associated with this group. Table 2 highlights the most relevant, confirming well-known pathways and suggesting possible new fields of study in this context.

3. Environmental factors and TFs in Psychiatric Disorders

Since the discovery of the lac operon system in E. *coli* – the first demonstration of how the transcription machinery works in different environmental contexts (Jacob and Monod, 1961) – several other examples were described in different organisms like fungi (Vicentefranqueira et al., 2018), plants (Song et al., 2016), and animals (Pat

Willmer, 2004) in situations like temperature variation, stress response, immune system modulation and others.

The challenge behind the search for risk factors in psychiatric disorders is understanding how different interactions may converge to a similar outcome. Environmental factors can cause a significant impact on the onset of NDDs along with genetic risk factors (discussed in section 2). Alterations in TFs may be a common point in this multifactorial universe of NDD triggering. In this section, environmental risk factors are discussed, focusing on possible roles in NDDs and psychiatric disorders.

3.1 Maternal Immune Activation

Maternal immune activation (MIA) is associated with the onset of disorders such as ASD and schizophrenia (Fontes-Dutra et al., 2020). MIA induction by poly(I:C) exposure enhanced PAX6 (paired box 6) expression in mice embryos resulting in cell cycle impairments, and increased number of cortical neurons expressing COUP-TF interacting protein 2 (CTIP2) in deeper layers (V and VI) (Ben-Reuven and Reiner, 2019). In a complementary finding, *in vitro* exposure of neuronal progenitors to high doses of IL-6 (mimicking MIA) increased STAT3 (signal transducer and activator of transcription 3) phosphorylation and reduced the differentiation of neurons that express CTIP2 and TBR1 (T-box brain transcription factor 1) (Zuiki et al., 2017). We hypothesize that these differences occur due to the TFs activated in each model: enhanced PAX6 expression, a pivotal regulator of neuronal processes, is associated with increased CTIP2+ cells since this TF is a major regulator of deeper cortical layers. On the other hand, IL-6 leads to the activation of STAT3, which, in neural progenitors, was already associated with increased astrocytogenesis and suppressed neurogenesis (Hong and Song, 2015, Chen et al., 2014), explaining the decreased number of neuronal cells expressing CTIP2 and TBR1.

MIA-induced by poly(I:C) in mice increased REST/RE-1 (RE-1 silencing transcription factor) expression, resulting in decreased expression of KCl cotransporter, delaying the switch of GABA function from excitatory to inhibitory in mice embryos (Corradini et al., 2018). In addition, a decreased forebrain expression of ARX (aristaless related homeobox), was associated with PV+-neurons impairments (Nakamura et al., 2019) in the same model. In an LPS-induced MIA, the fetus presented reduced expression of the TFs *Dlx* 1, 2, and 5 (distal-less homeobox), which are involved in the generation and migration of GABAergic interneurons (Oskvig et al.,

2012). Finally, MIA-induced microglial activation was influenced by the decreased expression of the TF *Pu.1* (transcription factor PU.1) - in this case, epigenetic changes impaired the expression of this TF (Mattei et al., 2017; Yeh and Ikezu, 2019).

Some viral infections are also described as environmental risk factors during pregnancy. For example, the STAT-binding V protein, an important virulence factor in the rubella infection, can impair the functions of STAT, a TF involved in interferon signaling and synaptic plasticity processes (Ramachandran et al., 2008). Also, the rubella virus itself can interfere in the expression of *Rax* (retina and anterior neural fold homeobox) and S*ix3* (sine oculis homeobox homolog) TFs (Bilz et al., 2019), importantly related to eye and brain development. In neural progenitor cell culture, the cytomegalovirus early protein 1 (IE1) decreased *Sox2* expression by inhibiting phosphorylation of STAT3 (Wu et al., 2018) and downregulated *Hes1* (Hes family BHLH transcription factor 1) (Liu et al., 2017; Wu et al., 2018), leading to cell cycle and migration disturbances.

3.2 Effects of Teratogens

The environmental risk factors during pregnancy (Lein, 2015) also include chemical treatments such as the antiepileptic valproic acid (VPA), a well-demonstrated risk factor to ASD (Christensen et al., 2013). Adult hippocampal neural progenitors exposed to VPA *in vitro* increased the expression of *NEUROD1*, a TF involved in neuro/glial differentiation (Hsieh et al., 2004). In a complementary way, mice embryos exposed to VPA upregulated *Pou3f1* and *Sox4,* downregulated *Egr2* (growth response protein 2) (Okada et al., 2005), and altered the expressions of neurogenin 2 (NGN2), NEUROD1, and PAX6 (Kim et al., 2014) in a time-dependent way. Interestingly, PAX6 alterations (like increased acetylated histone binding to the gene promoter region), which were more prominent, are related to the VPA histone deacetylase (HDAC) inhibition feature (Kim et al., 2014). Moreover, postnatal analysis of mice exposed to VPA during pregnancy showed decreased expression of *Hes1* and *Pax6* mRNA in the cerebral cortex, suggesting a possible long-term effect of these TFs in brain development (Kawada et al., 2018). The set of evidence emphasizes the major impact of VPA in the TF machinery associated with cell cycle, apoptosis of neural tube cells, histone modulation, and brain organization.

Ethanol (Et-OH) consumption during pregnancy causes fetal alcohol syndrome (Gupta et al., 2016), a disorder that shares several features with ASD. Similar to VPA,

Et-OH impairs *Pax6* expression in murine embryos (Aronne et al., 2008) and disrupts correct cell lineage differentiation, mainly by modulation of POU5F1 and SOX2 (Sánchez-Alvarez et al., 2013). In a study using zebrafish embryos exposed to Et-OH, besides *sox2*, sixty TFs associated with gastrulation processes demonstrated altered expression (mostly downregulated) (Sarmah et al., 2020). Interestingly, both human progenitor neural cells and mouse embryos demonstrated abnormal activation of HSF1 (heat-shock transcription factor 1), leading to neuronal migration impairments and periventricular heterotopia (Ishii et al., 2017).

Folate intake during pregnancy is necessary to prevent neural tube-associated alterations like spina bifida and myelomeningocele (Pachón et al., 2013); however, the regulation of dosage is essential since high doses are potentially deleterious (Mudryj et al., 2016). An *in vitro* study demonstrated that folate receptors, which have TF function, regulate the expression of other TFs involved in neurodevelopment like *Sox2* and *Klf4* (kruppel like factor 4) (Mohanty et al., 2016). Interestingly, in a neural tube defect animal model based on the deletion of *Pax3*, supplementation with folate restored the proliferative status of the neuroepithelium, demonstrating a possible common pathway regarding PAX3 and folate signaling (Sudiwala et al., 2019). Analysis of DNA methylation patterns in blood and tissue from the human umbilical cord demonstrated that folate deficiency during pregnancy is associated with methylation alterations in HOX, LIM, PAX, and TBOX TF families (Sakurai et al., 2019). On the other hand, excessive supplementation in mice induced dysregulated expression of *Fos* (FBJ osteosarcoma oncogene), *Maff* (MAF B ZIP Transcription Factor F), and EGR2, in addition to inducing behavioral and weight alterations (Chu et al., 2019).

3.3 Lesion Events

Perinatal complications like fetal or early postnatal hypoxia are also associated with neurodevelopmental impairments and expression changes in TFs, especially in the hypoxia-induced factors (HIF) (Dengler et al., 2014). The expression of HIF-2α, in vitro, upregulated the solute carrier transporter 7a5 (SLC7A5) in differentiated neuronal cells, followed by impaired transport of branched-chain amino acids in the brain (Onishi et al., 2019) - a feature already described in ASD (Maynard and Manzini, 2017). While early postnatal hypoxia in mice decreased expression of Olig2 (oligodendrocyte transcription factor 2) (van Tilborg et al., 2018), transient hypoxia in

postnatal day 7 induced a complex time-course pattern of high and low expression of Olig2, Ascl1, and Nkx2-2 (NK2 Homeobox 2) TFs, followed by oligodendrocyte maturation impairment (Affeldt et al., 2017). Finally, GWAS comparison of schizophrenia and hypoxic-ischemic response associated genes in humans demonstrated significant overlap of changes in TFs like TCF4 and ZEB2 (zinc finger E-box binding homeobox 2) (Schmidt-Kastner et al., 2020). The compilation of all TF described in the "Environmental factors and TF in Psychiatric Disorders" section was submitted to Reactome® (Wu and Haw, 2017) analysis resulting in a demonstration of enriched biological pathways associated with this group. In Table 3, the most relevant are highlighted, demonstrating important overlays with ASD and schizophrenia.

4. NDD-associated multifactorial disorders

This section discusses ASD and schizophrenia, two disorders with an intricate contribution of both genetic and environmental risk factors. The diversity of effects in the TFs may be associated with the broad spectrum within the disorders and the interaction between genes and environment throughout the neurodevelopmental timeline.

4.1 Autism Spectrum Disorder (ASD) and TFs

ASD is a multifactorial NDD determined by a set of characteristics, including stereotyped or restricted behaviors and impairments on social interaction and communication (American Psychiatric Association, 2013). Genetic studies analyzing populations or families with ASD cases already demonstrated many alterations in TFs associated with neurodevelopment. One study comparing autistic subjects with unaffected siblings, focused on 64 genes implicated in neurodevelopment, highlighted mutation events in nine genes, three being TFs: *TBR1*, *ADNP* (activity-dependent neuroprotector homeobox), and *PAX5* (O'Roak et al., 2014).

Alterations in *TBR1* are classically related to ASD (O'Roak et al., 2012), and, more recently, mutations in this gene were also associated with neocortical malformations in humans (like pachygyria) (Nambot et al., 2020; Vegas et al., 2018). Furthermore, in animal models, loss-of-function or deletion of TBR1 resulted in connectivity issues in layer VI neurons from the neocortex (Fazel Darbandi et al., 2018). These cells also presented disrupted expression of the laminar identity markers

(Bedogni et al., 2010), indicating the contribution of TBR1 during neuronal migration and cortical organization.

Critical mutations on *ADNP* are described in the Helsmoortel-Van der Aa syndrome, a rare condition with substantial overlap with ASD (Arnett et al., 2018). ADNP can play essential roles in autophagy (Sragovich et al., 2017), cell cycle regulation (Mollinedo et al., 2019), neuronal migration, and maturation (Helsmoortel et al., 2014). In animal models and clinical studies, supplementation with peptides derived from ADNP demonstrated interesting neuroprotective results (regulation of glutamatergic synapses and microtubule conservation, for example) in ASD (Gozes et al., 2009; Javitt et al., 2012; Sragovich et al., 2019).

Finally, *PAX5* has recently emerged as a gene associated with ASD, with incipient descriptions of its function during neurodevelopment. The deletion of *PAX5* in GABAergic neurons led to malformations in the ventricles, triggering a hydrocephalus-like condition, which may imply that this factor is pivotal in processes like neuron maturation and cytoarchitecture organization (Ohtsuka et al., 2013).

In the Lamb-Shaffer syndrome, a disorder associated with autistic traits, several microdeletions and truncating variants in *SOX5*, were observed (Zawerton et al., 2020). The attenuation in the expression of the *SOX5* gene in different brain regions seems to be related to splicing alterations and the generation of regulatory molecules like lncRNA (Parikshak et al., 2016). *Sox5*-null mice displayed an immature pattern of layer VI neuron expression, as well as impairments on corticothalamic connectivity, demonstrating important roles of this factor on corticogenesis (Kwan et al., 2008).

The impairments of several neurotransmitter systems in ASD are widely described and these changes may involve several TFs. Biallelic disruptions in RARB (retinoic acid receptor beta) and FEV (fifth ewing variant protein) were identified as altered in ASD (Doan et al., 2019). RARB targets were altered both in animal models and humans, demonstrating the translation in RARB alterations mediating the retinoic acid pathway (Moreno-Ramos et al., 2015), while FEV is mainly expressed in raphe nuclei (Iyo et al., 2005), especially in serotonergic neurons (Maurer et al., 2004), being necessary for both the differentiation and the synthesis of serotonin. Finally, a meta-analysis of GWAS studies demonstrated significant alterations in the *PITX3* (paired like homeodomain 3) gene (The Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017), a TF that is related to the differentiation of dopaminergic neurons (and dopamine synthesis) in the midbrain, and was already

described in the context of Parkinson disease (Li et al., 2009) and ocular developmental defects (Zazo Seco et al., 2018).

Recently, new TFs were described in the context of ASD, including SHOX (short stature homeobox) (Tropeano et al., 2016), a TF associated with short stature disorders (Fukami et al., 2016), and ZNF292 (zinc finger protein 292), both TFs with important expression in the developing brain (Mirzaa et al., 2020) (Durand et al., 2011). The possible roles of these TFs in NDD are still to be unveiled.

Moreover, alterations in the interaction components of TFs were described as relevant in the context of ASD. A specific SNP was associated with less DNA binding of MAZ (MYC associated zinc finger protein), resulting in lower expression of oxytocin receptor (OXTR) gene and possibly contributing to impairments in the oxytocin signaling (de Oliveira Pereira Ribeiro et al., 2018), suggesting a new mechanism behind oxytocin questions in ASD. In addition, an up-regulation of *ATF6* (activating transcription factor 6) was observed in the *postmortem* hippocampus of ASD patients (Dong et al., 2018). This TF interacts with misfolded proteins, inducing chaperone transcription (Adachi et al., 2008).

4.1.1 TF roles in the neuroimmune component of ASD

In addition to the neurodevelopmental impairments, changes in the immune system (including neuroinflammation) play an important role in ASD, being often described as a hallmark of this disorder (Deckmann et al., 2018; Gottfried et al., 2015; Masi et al., 2017; Siniscalco et al., 2018). Interestingly, several TFs also mediate these neuroimmunological issues. Recently, NRF2 (nuclear factor, erythroid 2-like 2) - a basic leucine zipper TF that protects the immune cells against inflammation and pro-oxidating agents - was downregulated in monocytes of ASD subjects, whereas inflammatory (NF*k*B, IL-6, IL-1β) and nitrative stress (iNOS, nitrotyrosine) parameters were increased (Nadeem et al., 2020).

The T-bet (T-box transcription factor 21), GATA3 (GATA-binding protein 3), STAT3, RORγt (RAR-related orphan receptor gamma), and FOXP3 TFs play an important role in Th1 (T-bet), Th2 (GATA3), Th17 (STAT3/RORγt) and Treg (FOXP3) commitment lineages from naïve CD4+ T cells (Deckmann et al., 2018). Peripheral blood mononuclear cells (PBMC) from ASD patients demonstrated lower levels of FOXP3 and higher levels of RORγt/STAT 3, T-bet, and GATA3, together indicating a deficit in Treg differentiation and an imbalance of TFs related to Th1/Th2/Th17

response (Ahmad et al., 2017c). Besides that, HELIOS (expressed by FOXP3+T cells and associated with T cell differentiation) was downregulated, both in mRNA and protein expression levels, suggesting that this TF is pivotal in the ASD immune imbalance (Ahmad et al., 2018e). Likewise, granulocyte-macrophage colony-stimulating factor (GM-CSF) expressed by CD45 cells was increased in children with ASD, whilst numbers of CD45+HELIOS+ and CD45+Stat6+cells were lower, corroborating the involvement of TFs in the regulation of the immune system and demonstrating the need for further investigations (Ahmad et al., 2020).

Another interesting animal model to ASD study is the BTBR T+ Itpr3tf/J (BTBR), a genetic model that presents low levels of social behavior and high levels of repetitive behavior (Ryan et al., 2019). CD8+T cells from BTBR animals produced higher levels of IL-17A, RORγT, IL-22, T-bet, and STAT3 and lower levels of inducible costimulator (ICOS) and FOXP3. CD4+ T cells, in turn, produced elevated levels IL-17A, IL-21, IL-22, IFN-γ, T-bet, RORγt, and STAT3, and diminished levels of FOXP3 and HELIOS (Ahmad et al., 2018b, Ahmad et al., 2018c, Ansari et al., 2017). Alterations in mRNA and protein expression levels of IL-17A, RORγT, IL-22, T-bet, STAT3, pSTAT-3, IL-10, and FOXP3 were observed in the brain tissue (Ahmad et al., 2019).

BTBR mice also exhibited decreased CD4+IL-21+, CD4+IL-22+, CD4+GATA3+, and CD4+T-bet+, and increased CD4+CTLA-4+ (cytotoxic T lymphocyte-associated gene-4) expression in spleen cells, in addition to increased mRNA and protein expression levels of IL-21, IL-22, GATA3, and T-bet in brain tissue (Ahmad et al., 2017a). Departing from previous evidence, BTBR mice showed lower levels of FOXP3+ and higher levels of T-bet+, GATA-3+, and RORγt+ production in CD4+ T cells (Bakheet et al., 2017), shedding light on how the BTBR animal model reproduces the complexity in immune impairments observed in ASD subjects.

When the neuroimmune response mediated by toll-like receptors (TLR), NF-κB signaling, nitric oxide synthase (iNOS), and cyclooxygenase (COX-2) expression was evaluated, results showed elevated CD4+TLR2+, CD4+TLR3+, CD4+TLR4+ CD4+NF-κB+, and CD4+iNOS+ levels in spleen cells and increased TLR2, TLR3, TLR4, NF-κB, iNOS, and COX-2 mRNA expression levels in brain tissue (Ahmad et al., 2018a). Further, BTBR mice showed increased levels of IL-6+, TNF-α+, IFN-γ+, and STAT3+ in CD4+ spleen cells, and increased both mRNA expression and protein expression of IL-6, TNF-α, IFN-γ, JAK1, and STAT3 in brain tissue (Ahmad et al., 2018d). Altogether, these recent studies demonstrate an important connection

between TFs and the neuroimmune alterations present in ASD, with interesting evidence of diminished Treg and increased Th1/Th17 responses, suggesting new targets for study.

4.1.2 Complementary evidence of TF in ASD animal models

Animal models are pivotal to understand the biological pathways altered as a result of genetic issues. CHD8 haploinsufficiency in mice triggered ASD-like behaviors, such as repetitive behavior and impaired sociability. CHD8 acts by remodeling the chromatin through ATP-dependent activity, regulating the expression of many genes, such as β-catenin (Katayama et al., 2016), which has a pivotal role in the canonical WNT signaling pathway - directly implicated in ASD pathophysiology (Kwan et al., 2016). In addition, CHD8 mutations were associated with neurodevelopmental delay and abnormal activation of REST - a known neuronal gene regulator capable of physically interacting with CHD8 (Katayama et al., 2016). This is particularly interesting since it suggests a significant association between two genes in ASD, a chromatin remodeler (CHD8) and a TF (REST). Thus, the ASD pathophysiology could (at least partially) be explained by the remodeling of chromatin, facilitating the transcription of specific genes that may be related to the onset of this disorder.

Brain alterations related to changes in TFs include cortical and hippocampal structure, synaptic composition, and neuronal maturity and function – critical events in several psychiatric conditions. This is the case of EN2 (engrailed homeobox 2), a TF with conflicting associations with ASD in humans (Benayed et al., 2009; Gharani et al., 2004; Yang et al., 2008). In mice, knockout of *En2* resulted in several ASD-like behavioral alterations, including loss of sociability and impairments in fear conditioning and water maze learning (Brielmaier et al., 2012). In the same model, a reduction in the mRNA expression of GABAergic markers in the cortex and hippocampus (Sgadò et al., 2013) was observed, suggesting that these impairments might be time and layer-dependent (Allegra et al., 2014), which should be considered in the studies with humans. In addition, recent evidence demonstrates alterations in sensory features in *En2*-null mice, including impaired processing of taste (Gupta et al., 2018) and reduced connectivity in the somatosensory cortex, combined with increased activity of the basolateral amygdala after sensory tasks (Chelini et al., 2019). These data indicate a possible increased aversion component in the context of non-aversive sensory stimuli,

which is typical in ASD (Balasco et al., 2020). Finally, other aspects like decreased serotonin content (more critical at a young age) in the cerebellar cortex (Viaggi et al., 2015) and monoamine system impairment were already described (Genestine et al., 2015).

In rodent models, conditional alteration of *Tshz3* (teashirt zinc finger homeodomain 3) is explored as a translational approach to the 19q12q13.1 heterozygous deletion syndrome, a condition that shares similarities with ASD (Chowdhury et al., 2014). In this scenario, the haploinsufficiency of *Tshz3* in mice decreased the interest in social novelty and increased stereotypy, downregulated genes associated with dendritic extension, neuronal glutamate release, and increased LTP in corticostriatal connections (Caubit et al., 2016). Moreover, approximately 50% of the affected genes have a human ortholog described in ASD, highlighting glutamatergic synapses as a key subject in this model (Chabbert et al., 2019).

The presence of an SNP in a regulatory element, called I56i, identified in ASD patients (Hamilton et al., 2005) decreased DLX5/6 transcriptional activity in GABAergic interneurons from embryonic to postnatal life (Poitras et al., 2010), impairing cell migration, maturation, and survival (Lindtner et al., 2019). Another TF demonstrated significant action in these neurons: FOXG1 upregulation increased the number of GABAergic neurons in organoids derived from ASD patient cells (Mariani et al., 2015). In mice embryos, heterozygous loss of FOXG1 impaired dendritic morphology and neuronal migration in cortical neurons (Li et al., 2019b).

VPA-exposed rat offspring showed increased PAX6 expression, with higher postnatal glutamatergic neuronal differentiation, possibly related to the VPA-induced HDAC inhibition (Kim et al., 2014). Moreover, propionic acid-exposed animals decreased the expression of TCF4 in the hippocampus, resulting in granule cell impairments (Choi et al., 2018). TCF4 alterations, although more prominent in schizophrenia, have relevance in ASD: gain of function of TCF4 impairs the prefrontal cortex, with disruption of columnar organization of layers II/III, as observed in ASD patients (Page et al., 2018b). Moreover, a chromatin immunoprecipitation study demonstrated that TCF4 also binds to different sites associated with ASD (Forrest et al., 2018).

The compilation of all TF described in the “Autism Spectrum Disorder and TFs” section was submitted to Reactome® (Wu and Haw, 2017) analysis resulting in a demonstration of enriched biological pathways associated with this group. Table 4

highlights the most relevant, like the immune system, gene transcription, protein metabolism, cell signaling, and development.

4.2. Schizophrenia and TFs

Schizophrenia is a disorder characterized by the presence of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (American Psychiatric Association, 2013).

The *SOX11* gene was identified as a candidate gene for greater susceptibility to schizophrenia in a GWAS study in the Chinese Han population (Sun et al., 2020). SOX11 is expressed early in development, playing roles in cell fate, survival, and differentiation during neurodevelopment and organogenesis (Angelozzi and Lefebvre, 2019; Chew and Gallo, 2009). Moreover, a meta-analysis of GWAS found an overlap in regions implicated in schizophrenia and ASD in *FOXP3* and ATPase plasma membrane Ca2+ transporting 2 (*ATP2B2*) genes (The Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017). This is particularly interesting since FOXP3 is an essential regulator of the immune system (Taylor et al., 2020), and ATP2B2 regulates intracellular calcium homeostasis, necessary for appropriate synaptic connections (Yang et al., 2013).

In addition, the GWAS study pointed to genetic correlations of neurodevelopmental genes such as exostosin glycosyltransferase 1 (*EXT1*), astrotactin 2 (*ASTN2*), mono-ADP ribosylhydrolase 2 (*MACROD2*), and HDAC4 with schizophrenia and ASD. EXT1 gene is related to heparan sulfate synthesis, presenting a higher expression profile during the early postnatal period in the brain (mainly in the cortex and hippocampus formation) and around birth in the cerebellum (Inatani and Yamaguchi, 2003). Altered copy number variations (CNV) of the ASTN2 gene - involved in recycling vesicles in cerebellar neurons, (Behesti et al., 2018) - are associated with NDDs, such as ASD. MACROD2 regulates the processes involved in mono-ADP-ribosylation (Žaja et al., 2020). It is expressed in neuronal cells at embryonic day 16.5 and reaches the peak of expression at postnatal day 8, especially in the cortical layers II–V, and then gradually decreases through P30 (Ito et al., 2018). Lastly, HDAC4 plays a significant role in gene expression regulation related to synaptic plasticity, neuronal survival, and neurodevelopment (Ronan et al., 2013; Wu et al., 2016).

Several *postmortem* studies elucidated important region-specific features in the context of psychosis and schizophrenia. SP1 and SP4 (Sp transcription factor) are zinc-finger TFs with increased levels in the hippocampus and the cerebellum of chronic schizophrenia patients (Pinacho et al., 2014). The blockage of NMDAR caused similar alterations in these factors, suggesting involvement in glutamatergic pathways. Moreover, SP4 has been described as a GABAAR regulator, highlighting the possible influence on E/I balance (Pinacho et al., 2015).

A recent study showed differential expression patterns and rare variants in genes related to neural cell genesis and glial differentiation in individuals with schizophrenia (Chen et al., 2018). One of these genes was the *Pou3f2* gene, a TF involved in cognitive function and adult hippocampal neurogenesis (Hashizume et al., 2018). Interneurons also seem to be affected by disturbances in TFs: an analysis of the prefrontal cortex from schizophrenia patients demonstrated an elevation in the expression of *MAFB* and the coactivator PGC-1α (Volk et al., 2016), which are deeply related to PV and SST development and function, suggesting possible immaturity of these cells or compensatory mechanisms.

NPAS4 (neuronal PAS domain protein 4) is a brain-specific TF that can modulate schizophrenia symptoms (Alachkar et al., 2018; Shepard et al., 2019). This protein is present in both excitatory and inhibitory neurons, regulating the excitability by increasing the activity of the interneurons in neural circuits (Spiegel et al., 2014). The deficiency of NPAS4 affects the expression of many GABAergic targets in the prefrontal cortex (PFC), such as PV and GAD67 (Shepard et al., 2017). When combining NPAS4 deficiency and adolescent stress, mice showed altered performance in cognitive flexibility on the extra-dimensional set shift task and altered expression in GABAergic markers (Page et al., 2018a).

Npas4 wild-type mice showed a decreased percentage of PV cells in PFC after adolescent stress when compared to heterozygous mice (Page et al., 2018a). Moreover, the relation between NPAS4 expression and behavioral alterations was confirmed using transgenic Cre-Lox mice, elucidating the contributions of NPAS4 in the regulation of excitatory and inhibitory balance, as well as in behavior in schizophrenia animal models (Shepard et al., 2019).

LHX6 presents a cysteine-rich zinc-binding domain, the LIM domain, whereas SOX6 presents a conserved high mobility group (HMG) DNA-binding in the minor groove of DNA. Altogether, both LHX6 and SOX6 regulate crucial neurodevelopmental

processes, such as specification, migration, and maturation of PV and SST neurons (Volk et al., 2012). In *postmortem* samples of PFC from individuals diagnosed with schizophrenia, reduced mRNA levels of *Lhx6* and *Gad67* were found, but there were no significant differences of *Sox6* and calretinin (Volk et al., 2012). Furthermore, in a cohort of schizophrenia individuals, reduced levels of *Lhx6* and *Gad67* mRNA levels were observed in the cortex. In parallel, the same study evaluated monkeys throughout postnatal life, pointing out declining levels of LHX6 from perinatal to prepubertal life (Volk and Lewis, 2014). These crucial data highlight the important roles of LHX6 in GABAergic alterations in the pathophysiology of schizophrenia.

Another signaling pathway implicated in many NDDs is the JAK/STAT1, with roles regarding the activation of a proinflammatory profile in circulating immune cells (Ahmad et al., 2017b; Sharma et al., 2017). Recently, a study measuring the activation of this pathway in individuals with psychosis, early in the illness and hospitalized with acute exacerbation of psychosis, showed that JAK-STAT1 related gene expression is suppressed in both groups. The expression normalized in individuals with chronic or longer illness duration, indicating a temporal and contextual regulatory profile of JAK/STAT1 signaling pathway and highlighting roles of the immune system in the pathophysiology of schizophrenia (Melbourne et al., 2019).

Like animal models, *in silico* approaches can provide relevant information and mechanistic evidence about the roles of TF in neurodevelopment. A recent study, which analyzed neuronal migration and corticogenesis data, identified eight functional modules involving Disrupted-in-schizophrenia 1 (DISC1) gene and its interacting proteins that regulate neuronal migration processes, such as STAT3, TCF3, and TAL1 (John et al., 2019).

4.2.1 The prominent role of TCF4 in schizophrenia

In the context of schizophrenia, one TF has particular relevance: TCF4. TCF4 is known to be intimately related to PTHS (Amiel et al., 2007), and interestingly, in schizophrenia, many altered biological pathways have a significant association with this TF. Since the late 2000s, when the first study associating alterations in TCF4 and schizophrenia was released (Stefansson et al., 2009), several other studies consolidated and demonstrated the relevance of TCF4 in psychotic episodes and bipolar disorder (Gao et al., 2020; Hall et al., 2014; Ripke et al., 2014; Steinberg et al., 2011).

In animal models, it was demonstrated that overexpression of TCF4 in mice resulted in sensorimotor and fear conditioning impairments, highlighting the relevance of TCF4 in cognitive processes (Brzózka et al., 2010, Brzózka et al., 2016; Brzózka and Rossner, 2013). Analysis of *Tcf4* polymorphisms in humans with schizophrenia confirmed the influence of this TF in processes like verbal declarative memory (Lennertz et al., 2011), attention-related tasks (Zhu et al., 2013), problem-solving tasks (Albanna et al., 2014), and lower cognitive performance (Hui et al., 2015). In addition, TCF4 mRNA levels were related to positive- and negative-symptoms (Wirgenes et al., 2012), and cognitive impairments (Alizadeh et al., 2017), consolidating the role of this TF in high-functioning integrative processes.

Knockdown of *Tcf4* in neural-lineage cells increased transcription of genes related to cell cycle control, specifically proliferation (Hill et al., 2017). Besides that, phosphorylation promoted by protein kinase A (PKA) also seems to be related to the TCF4 activity both *in vitro* and *in vivo* in response to Ca^{2+} influx (Sepp et al., 2017). Likewise, the WNT/β-Catenin pathway also influences the transcription and activity of *Tcf4* since the activation of WNT/β-Catenin mediated by pharmacological intervention increased TCF4 mRNA levels (Hennig et al., 2017). Some evidence involving changes in WNT/β-Catenin pathway and schizophrenia includes shortening of cell cycle (Fan et al., 2012), weakening of the blood-brain-barrier associated with alterations in PKA (Nishiura et al., 2017), and disruptions in glutamatergic signaling (Uematsu et al., 2015; Zhao et al., 2019). Complementary evidence of disruption in the WNT pathway includes hyperactivation in the presence of DISC-1 (Brandon et al., 2009), imbalance between canonical and non-canonical signaling, and altered mRNA levels of WNT-related genes (Hoseth et al., 2018). Therefore, TCF4 may be the convergent point of relevant alterations in the context of neurodevelopment, synaptic plasticity, and cell signaling.

The necessity to understand how TCF4 works in the context of other genomic alterations in schizophrenia was clarified by wide chromatin immunoprecipitation (ChIP) assays and *in silico* approaches. The identification of TCF4 in a ChIP assay in SH-SY5Y cells demonstrated that this TF is majorly related to genes involved in axonal and neuronal development, especially those expressed in the pyramidal neurons of the somatosensory cortex. Additionally, the results also confirmed prior studies that suggested targets of TCF4 by using interference RNA techniques or *postmortem* transcriptomic analysis of patients with schizophrenia (Xia et al., 2018). A

transcriptional analysis of the dorsal PFC and olfactory neuroepithelium of schizophrenia subjects demonstrated that TCF4 is a major regulator in transcriptional networks in both regions. When comparing cell lineages with TCF4 knockdown, the impact on these networks was increased in neuronal progenitor lineages compared to mature glutamatergic neurons, suggesting that TCF4 may be pivotal in early developmental processes (Torshizi et al., 2019).

TCF4 studies faced a vital limitation in animal models: homozygous knockout was extremely deleterious, resulting in the death soon after birth (Forrest et al., 2013). *Tcf4* haploinsufficiency in mice resulted in substantial behavior impairments, such as in social interaction, vocalization, fear conditioning, learning, and memory, which are improved by inhibiting or silencing HDAC function, suggesting a possible pathway involved in TCF4 action (Kennedy et al., 2016). A comparison between human and mouse embryos demonstrated that TCF4 is expressed in the same regions across time in both species (initially in transient regions of proliferation and then in neurons during migration) and has similar regulation by associated TF TCF3. TCF4 haploinsufficiency was also related to impairments on neuronal migration, cortical composition, and synaptic structure (Li et al., 2019a). Similarities between humans, rhesus monkeys, and mice regarding TCF4 alterations demonstrated structural brain abnormalities similar to PTHS (Jung et al., 2018).

Interestingly, a study with *Drosophila* demonstrated that silencing of *TCF4* orthologue *Da* resulted in synaptic and locomotor impairments (Tamberg et al., 2020). These results highlight the important conservation of TCF4 function in several species, especially regarding neurodevelopment. Although the animal models may be more related to PTHS, their insights about pathways involved in schizophrenia are fundamental to guide further investigations in this theme.

Genetic alterations are not unusual, and the interactions between may underlie several impairments. Disruption in two TFs relevant to schizophrenia (TNR1 and TCF4) resulted in a similar outcome in mouse primary neuronal cultures: decreased synaptic content and neuronal proliferation, probably associated with disruptions in syntaxin-mediated neurotransmitter release pathway (Rosato et al., 2019). Likewise, using *in silico* approaches, six genes (*CNTN4*, *GPM6A*, *MMP16*, *PSMA4*, *GATAD2A*, and *TCF4* - the last two are TF) are highlighted as a significant cluster associated with schizophrenia - when knockdown of this group was replicated in SH-SY5Y cells, major issues regarding proliferation were observed. This set of evidence brings attention to

the fact that polygenetic risks need to be considered to better understand the condition (Ma et al., 2018).

The compilation of all TF described in the “Schizophrenia and TFs” section was submitted to Reactome® (Wu and Haw, 2017) analysis resulting in a demonstration of enriched biological pathways associated with this group. Table 5 highlights the most relevant, like the immune system, gene transcription, cell signaling, and development.

5. Intellectual Disabilities (ID) and TFs

In this section, TFs related to ID, language impairments, and other characteristics not necessarily strictly associated with specific disorders are discussed since the pathways involved may be relevant in several conditions.

FOX proteins are a highly conserved group of TFs with many different functions including cell cycle regulation, energetic metabolism, and stress resistance (Golson and Kaestner, 2016). A subset of this group, FOXP, have important relations with cognitive processes, especially language and speech development (Hamdan et al., 2010; Lai et al., 2001).

Researchers observed an association of a family-related language impairment (which included speech and written alterations) with a missense mutation on the *FOXP2* gene that disrupted the DNA-binding domain (Lai et al., 2001). Since then, the “KE family” improved the understanding of the pathways behind language, and alterations in *FOXP2* were analyzed in several other disorders, including ASD and schizophrenia (Oswald et al., 2017). The mechanisms related to FOXP2 activity are still unclear; however, important animal studies brought insights regarding this theme.

An analysis in zebra finch demonstrated that both humans and songbirds have similar patterns of FOXP2 brain expression throughout development, especially in regions associated with sensorimotor integration, which are important in both species for the modulation of vocal expression (Teramitsu et al., 2004). Studies with *Foxp2*-mutations in mice showed important alterations in the basal ganglia regarding dopamine levels, synaptic plasticity, and neuronal morphology (Enard, 2011). Disruptions on cortico-basal ganglia circuits may be related to MEF2C (myocyte-specific enhancer binding factor 2C) TF, which represses striatal synaptic and spinogenesis and is repressed by FOXP2; thus, defects in FOXP2 may lead to a disinhibition of MEF2C (Chen et al., 2016). Additionally, FOXP2 also seems to increase GABAergic inhibition on D1 positive neurons in striatum, impairing the

dopaminergic signaling (van Rhijn et al., 2018) and playing important role in the maturation of excitatory cortical neurons (Hickey et al., 2019).

In the behavioral field, FOXP2 alterations were associated with social impairments (Medvedeva et al., 2019), probably related to modifications in the pattern of ultrasonic vocalizations (Chabout et al., 2016; Gaub et al., 2016). Interestingly, modifications in FOXP2 restricted to other structures like cartilage also caused impairments on vocalizations and motor skills, indicating a convergent role of this TF in brain circuitry and skeletal development (Xu et al., 2018).

FOXP1 descriptions in the context of psychiatric disorders started in 2009, with a report that a chromosomal deletion in this TF was associated with speech delay, muscular tone alterations, and malformations (Pariani et al., 2009). Although similar to FOXP2, when observing language impairments, FOXP1 demonstrated an important association with ID, autistic-like features, and epilepsy, which highlighted its global spectrum of action. Interestingly, recent articles observed that similar alterations in *FOXP1* and *FOXP2* resulted in different phenotypes: while FOXP2 seemed to be restricted to verbal impairments, FOXP1 was confirmed to cause more broad and severe issues in the context of the NDDs (Sollis et al., 2017). The fact that FOXP1 also interferes in language may be explained by its interaction with FOXP2: even when altered by mutations, FOXP1 retained the ability to interact with FOXP2, which may end up disrupting FOXP2 action (Sollis et al., 2016).

Homozygous brain loss of FOXP1 in an animal model resulted in a decreased number of neurons in the striatum and excitatory/inhibitory imbalance in the CA1 area of the hippocampus, as well as autistic-like behaviors including stereotypy and social impairments (Bacon et al., 2015). In addition, *FOXP1* deletion seems to disrupt the expression of genes related to synaptic plasticity, LTP, and spatial learning in the hippocampus and genes related to the identity of neurons of the somatosensory cortex (Araujo et al., 2017). Important alterations found in models with total or partial *FOXP1* deletion include reduced pup ultrasonic vocalization, and loss of the sex-associated differences in these vocalizations (probably by an interesting relation of FOXP1 and androgen hormones) (Fröhlich et al., 2017), in addition to motor issues related to gastrointestinal function (Fröhlich et al., 2019). Moreover, the ASD-related nonsense mutation in FOXP1 induced autophagy and impaired neuronal migration and dendritic morphology (Li et al., 2019b). Taken together, the present data highlight the variety of functions of FOXP1 in neurodevelopment - which probably are associated with

hippocampal and striatal function - suggesting that alterations in this TF may lead to a chain reaction that affects other TFs.

BCL11b (BAF chromatin remodeling complex subunit) is a zinc finger TF with important roles in the development of the immune system, especially the T lymphocytes lineage. Heterozygous mutation in this gene was associated with a severe combined immunodeficiency identified as Immunodeficiency 49, in which the patient presents features like cranial malformation and absence of corpus callosum (Punwani et al., 2016). Further studies demonstrated the presence of impaired speech, motor development, and intellectual disabilities in multiple types of mutations, with severity being associated with alterations within the DNA-binding site (Lessel et al., 2018; Prasad et al., 2020; Qiao et al., 2019). Although little is known about BLC11b specific mechanisms in NDDs, its function is already described in the context of spinal and neocortex development and hippocampal neurogenesis (Simon et al., 2020). Since this TF appears to be a link between immune and neurological development, understanding its functions in psychiatric disorders like ASD and schizophrenia is likely to be a very promising field of study.

6. Integrative Perspectives

The complexity regarding each cell fate involves a coordinated expression profile that can be altered in many ways. We observed that genetic structural alterations in TFs impair their functions significantly, especially when the DNA-binding domain is affected. Environmental factors also impair the functionality of TFs; however, the issue here seems to occur at the transcription level, probably altered by processes like epigenetic modifications and cell reprogramming.

The timing of the alteration also influences the major outcomes. By observing Figure 2, we can see that the TFs have important peaks of expression in the first or second trimester of pregnancy. In these moments, processes like neural proliferation and migration, microglia migration, astrocyte proliferation, oligodendrocyte formation, and synaptogenesis are guided by a strict time course of TFs expression. If a genetic alteration limits the TF, we can expect that all processes and other factors associated with it will be disorganized, inducing significant consequences. For environmental risk factors, the outcomes would primarily depend on 1) the duration of the risk factor exposure; 2) the number of pathways associated with the TF that are affected, and 3) the impacts on upstream and downstream elements. For example, if a relevant TF in

progenitor cells is affected, we expect considerable impacts in the whole lineage; conversely, if the alteration happens in more mature cells, we expect more specific impacts like the inability to develop full functionality.

Finally, the place or cellular type of occurrence indicates the most likely outcomes. Table 1 demonstrated that several TFs are highly expressed in embryo-fetal neural structures, especially in progenitor cells that will generate oligodendrocytes, astrocytes, GABAergic neurons, motor neurons, and others. For example, if a TF is highly expressed in the ganglionic eminence, we expect that alterations would induce significant impairments in GABAergic interneurons, the major population of cells originating from this region. Moreover, the basal expression of a TF is also fundamental to maintain cell programming, so alterations in other moments (for example, later periods of fetal life) may induce more subtle alterations that still have important effects.

In Figure 3, we observe the several interactions between all the TFs provided by String Database (Szklarczyk et al., 2019), highlighting that interference in one TF can disrupt many others – directly and indirectly. TFs like TCF4, PAX6, STAT, GATA, FOXP3, which are cited in several contexts (affected by environmental factors and also described in genetic and multifactorial disorders), are key points in the interaction map. Moreover, on the left side of the image, we can observe the distribution of the factors among the disorders, demonstrating important common points of TF involvement. Finally, from a biological pathway point of view, we can observe that, although the disorders are affected by different TFs, similar pathways are described (Tables 2-5), including transcription regulation, interleukin signaling, WNT/β-catenin signaling, cellular proliferation, activation of HOX genes and others, suggesting points of convergence in NDDs.

Thus, taken together, the body of evidence points to the fact that the broad spectrum of phenotypes observed in multifactorial disorders like ASD and schizophrenia may be associated with the alterations in TFs induced both by genetic and environmental triggers. Together with more specific studies of time-course and place of expression, the association among TFs will improve the understanding of major common points in the biological pathways, improving the knowledge about pathophysiology and possible therapeutic approaches in NDDs.

7. Concluding remarks

The complexity behind neurodevelopmental disorders and risk factors demands *in vivo*, *in vitro,* and *in silico* approaches to understand how biological pathways are disturbed in a context of genetic and environmental influences. The TFs comprise a diverse group of proteins with the ability to modulate RNA transcription, demonstrating an impressive time- and location-dependent organization, besides plasticity and susceptibility to possible context alterations. The present review compiled relevant data on literature regarding the expression and roles played by TFs during development in different NDDs and neuropsychiatric disorders, considering a multifactorial approach. Upon the observation of environmental risk factors and genome interactions, essential to the understanding of the final phenotypes of each disorder, we conclude that 1) TFs emerge as a point of convergence in NDDs, modulating neuroimmune alterations, disrupting processes like neuronal maturation, and causing anatomical changes; and 2) The analysis of TFs in psychiatric disorders is essential to shed light on molecular features of development still unknown and to expand the horizons for pharmacological interventions that can significantly improve the life quality of the affected individuals and their relatives.

8. Authors Contributions

JST and CG conceptualized the review. All authors contributed to the article and approved the submitted version.

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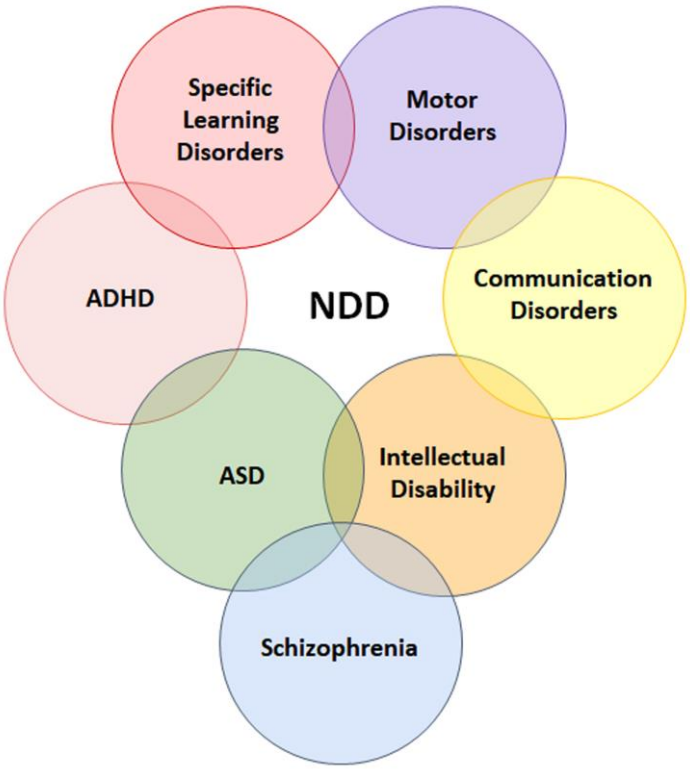

Figure 1: Diagram of neurodevelopmental disorders (NDD). Representation of the disorders included in the group of NDDs according to DSM-5, highlighting the chosen for this review.

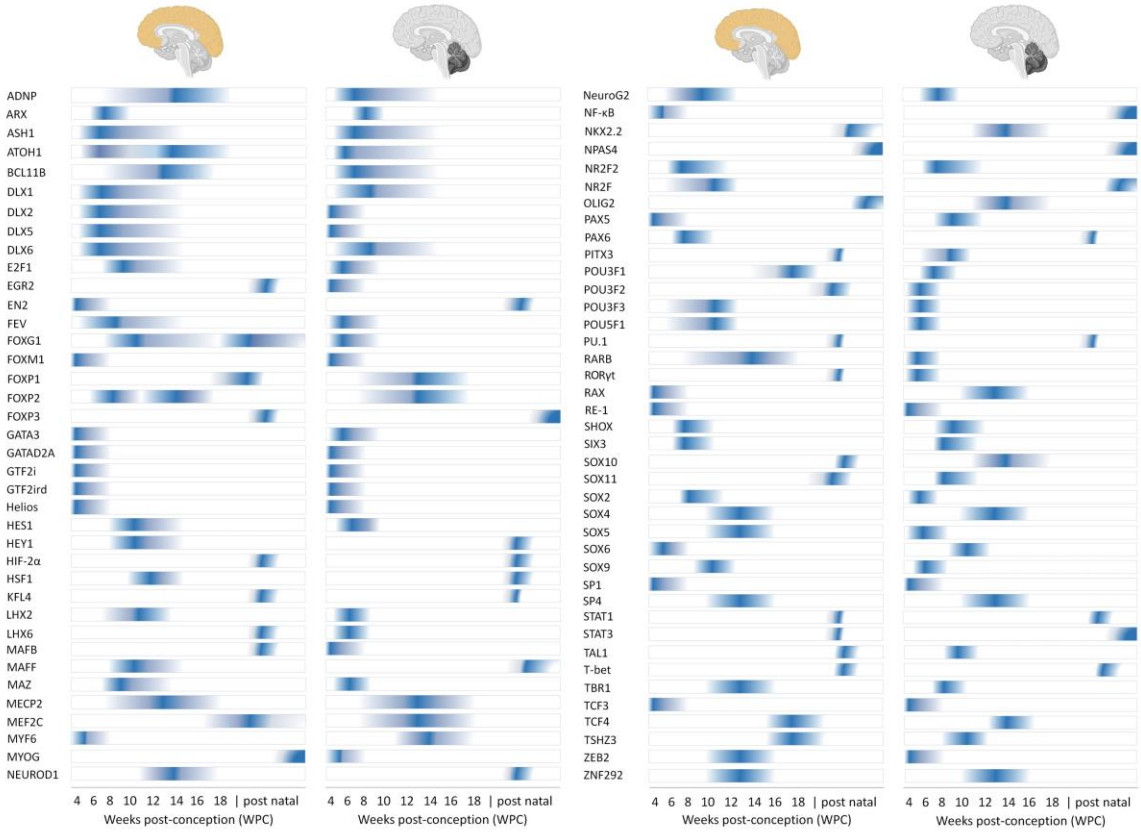

Figure 2: Time course of transcription factors expression. The double columns indicate patterns of expression in the human forebrain (left) and in the cerebellum (right). Blue gradient intensity is associated with expression peaks throughout time. Detailed information is available on Table 1. Adaptation from CARDOSO-MOREIRA, M. et al., 2019.

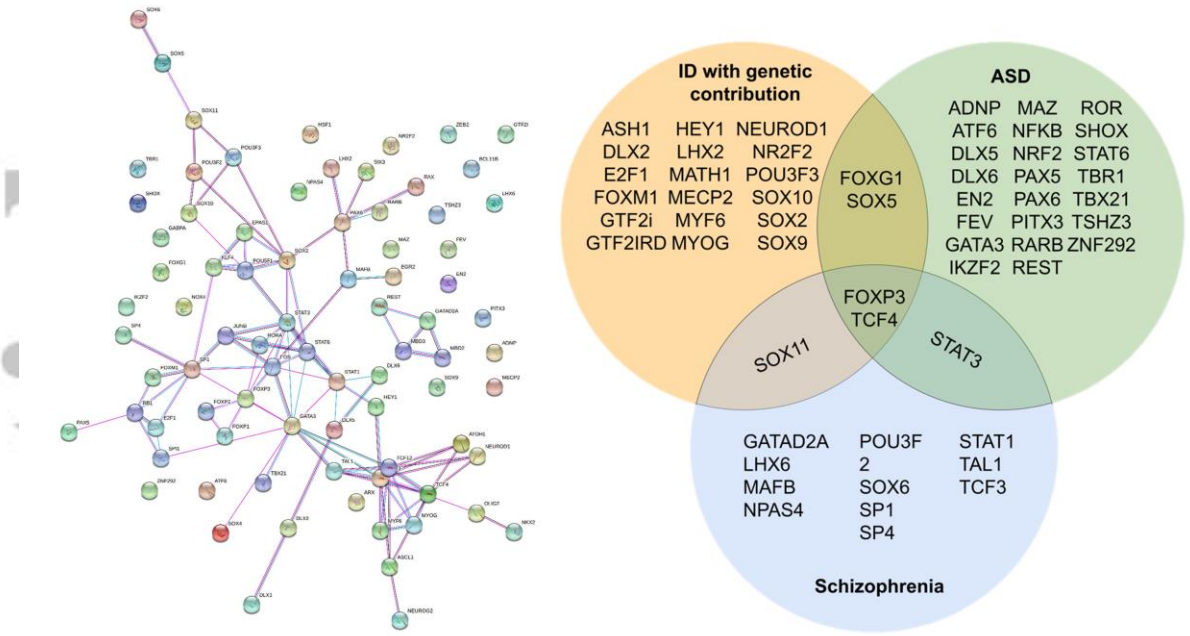

Figure 3: Interaction between transcription factors (TFs) distribution among the disorders. String Database map (Szklarczyk et al., 2019) demonstrates the interaction between all TFs listed in this review, while the Venn Diagram represents common and different points of TF involvement in the disorders discussed in this review. Black lines represent co-expression, cyan lines represent interactions observed in curated databases, and pink lines represent interactions observed experimentally.

Table 1: Compiled of all transcription factors addressed in this review. Information regarding DNA-binding sites was obtained from a database provided by LAMBERT, S. A. et al., 2018. TFs are represented in alphabetical order according to their classes. Regions or cells with high expression of the factors in embryos were described (In this context, nervous system, immune system, and eye were considered since they are associated with the scope of the review). Some TFs do not present a peculiar pattern of expression in these regions (for example, if the expression remains at similar rates throughout development), so they are described as "Low expression specificity". bHLH: basic helix-loop-helix; bZIP: basic leucine zipper domain; HMG: high mobility group box; WPC: weeks post conception; ZF: zinc finger. *GTF2i and GTF2ird had less information regarding time course of expression for humans, the represented data were obtained from mouse studies. Superscript numbers in the TFs indicate the section where they are cited and discussed. TFs complete denominations are described in Supplementary Table 1. ** The TF is considered a differential marker of the associated group of cells.

TF	Main DBD	Regions or Cells with high expression during embryo life
ASH1 / ASCL1 [2,3]	bHLH	**Brain:** Lateral, Medial and Caudal Ganglionic Eminence Progenitor Cells; d3**, d4** and d5** Neural Progenitor Cells; Anterior Entopeduncular Progenitor Cells **Eye:** Bipolar Precursor Cells; GABAergic Amacrine Cells; Rod Precursor Cells.
ATOH1/MATH1[2]	bHLH	**Brain**: Oligodendrocyte Precursor Cells**
HES1[3]	bHLH	**Nervous System**: Adult Oligodendrocyte Precursor Cells. **Eye**: Anterior Lens Epithelial Cells; Equatorial Lens Epithelial Cells; Late Retinal Progenitor Cells**; Muller Glia Precursor Cells**; Early Retinal Progenitor Cells**.
HEY1[2]	bHLH	**Nervous System:** Hypothalamus; Hippocampus; Thalamus; Cerebellum; Amygdala; Striatum; Medulla Oblongata; Cerebral Cortex; Pons
HIF-2α[3]	bHLH	Low expression specificity
MYF6[2]	bHLH	**Eye**: All Amacrine Cells
MYOG[2]	bHLH	Low expression specificity
NEUROD1[2,3]	bHLH	**Nervous System**: Primitive Spinal Cord; Mesencephalic Ventricular Zone; Telencephalon; Diencephalon; Metencephalic Alar Plate; Spinal Ventral Columns; Cerebellar Ventricular Zone; Spinal Dorsal Columns; Metencephalic Basal Plate; Epithalamus; Pituitary Gland; Cerebellum; Midbrain tegmentum; Lateral Ventricle **Eye:** AII Amacrine Cells; Bipolar Precursor Cells; Cone Precursor Cells; Mature Rod Bipolar Cells; Rod Precursor Cells; Mature Rod Cells;

NEUROG2[3]	bHLH	**Nervous System**: Meso-diencephalic Dopaminergic Precursor Cells **; Motor Neural Progenitor Cells **Eye**: Cholinergic Amacrine Cells; Bipolar Precursor Cells; Displaced Amacrine Cells; GABAergic Amacrine Cells; Dopaminergic Amacrine Cells
NPAS4[5]	bHLH	**Nervous System**: Amygdala, Anterior Cyngulate Cortex, Caudate, Frontal Cotex, Hippocampus, Hypothalamus, Nuclues Accumbens, Putamen, Substantia Nigra, Cerebellar Cortex
OLIG2[3]	bHLH	**Nervous System:** Oligodendrocyte Precursor Cells; MN Progenitor Cells**; Lateral, Medial** and Central Ganglionic Eminence Progenitor Cells; Anterior Entopeduncular Progenitor Cells; Neocortical Radial Glia Cells; Protoplasmic Astrocyte Cells
TAL1[5]	bHLH	**Nervous System**: V2 Neural Progenitor Cells**
TCF3[5]	bHLH	**Nervous System:** Oligodendrocyte Precursor Cells **Immune System**: Small Pre B-Cells; Pro B-Cells; B-cell Progenitor Cells; Large Pre B-Cells; Immature B-Cells
TCF4[2,4,6]	bHLH	**Nervous System**: Hypothalamus; Thalamus; Striatum; Medulla Oblongata; Cerebral Cortex; Midbrain tegmentum **Eye**: Amacrine Cells **Immune System**: pre Conventional Dendritic Cells; Plasmacytoid Dendritic cells; Mature B-Cells
MAFB[5]	bZIP	**Nervous System**: Roof Plate Cells; Cranial Neural Crest Cells. **Eye**: Anterior Lens Epithelial Cells
MAFF[3]	bZIP	**Nervous System:** Cerebral Cortex, Hippocampus, Basal Ganglia, Cerebellum Immune Cells: Granulocytes, NK cells
NRF2[4]	bZIP	Low expression specificity
BCL11B[6]	C2H2 ZF	**Immune System:** T Helper Cells; T-Cytotoxic Cells; Double Negative 2 Thymocytes
EGR2[3]	C2H2 ZF	**Nervous System:** Myelinating Schwann Cells**
Helios/ IKZF2[4]	C2H2 ZF	**Immune System**: T cells, B cells, Granulocytes
KLF4[3]	C2H2 ZF	**Immune System**: Macrophages
MAZ[4]	C2H2 ZF	Low expression specificity
RE-1 or REST[3,4]	C2H2 ZF	Low expression specificity
SP1[5]	C2H2 ZF	**Eye:** Fetal Corneal Basal Epithelial Cells; Keratocytes; Endothelial Cells; Keratoblasts
SP4[5]	C2H2 ZF	**Nervous System**: Hypothalamus; Hippocampus; Thalamus; Cerebellum; Amygdala; Striatum; Medulla Oblongata; Cerebral Cortex; Pons
TSHZ3[4]	C2H2 ZF	**Immune System**: Natural Killer Cells, Neutrophil
ZNF292[4]	C2H2 ZF	**Immune System:** pre–Conventional Dendritic Cells

ZEB2[3]	C2H2 ZF; Homeodomain	**Nervous System:** Myelinating Oligodendrocyte Cells
E2F1[2]	E2F	No differential expression during embryo stages
FEV[4]	Ets	**Nervous System:** Hypothalamus; Cerebellum; Amygdala; Cerebral Cortex; Midbrain tegmentum; Midbrain; Lateral funiculus; Midbrain; Basal Forebrain; Pons+Medulla;Septum;
PU.1[3]	Ets	**Immune System**: Small Pre B-Cells; Pro B-Cells Granulocytes; Osteoclast Precursor Cells**; B-cell Progenitor Cells
FOXG1[2,4]	Forkhead	**Nervous System**: Telencephalic Progenitor Cells**; Mature Endothelial Cells
FOXM1[2]	Forkhead	No differential expression during embryo stages
FOXP1[6]	Forkhead	**Nervous System:** Lateral motor column neuron-like cells
FOXP2[6]	Forkhead	No differential expression during embryo stages
FOXP3[2,4,5]	Forkhead	**Nervous System:** Hypothalamus **Eye:** Retina **Immune System:** CD4+ lymphocyte
GATA3[4]	GATA	**Immune System:** Hematopoietic Stem Cells**; Common Lymphoid Progenitor Cells**
GATAD2A[5]	GATA	No differential expression during embryo stages
GTF2[i2]	GTF2I-like	No differential expression during embryo stages
GTF2ird[2]	GTF2I-like	No differential expression during embryo stages
SOX10[2]	HMG/Sox	**Nervous System**: Oligodendrocyte Precursor Cells**; Schwann Precursor Cells**Diencephalic Neural Crest Cells**; Mesencephalic Neural Crest Cells**; Rhombencephalic Neural Crest Cells**
SOX11[2,5]	HMG/Sox	No differential expression during embryo stages
SOX2[2,3]	HMG/Sox	**Nervous System**: Bergmann Glia; Adult Neural Stem Cells **Eye**: Late Retinal Progenitor Cells Preplacodal Lens Ectoderm Cells Early Retinal Progenitor Cells Lens Placode Cells
SOX4[3]	HMG/Sox	**Nervous System**: Telencephalon; Metencephalic Alar Plate; Spinal Dorsal Columns; Metencephalic Basal Plate **Immune System**: Plasmacytoid Dendritic cells; Megakaryocyte-Erythroid Precursor Cells; Conventional Dendritic Cells II
SOX5[2,4]	HMG/Sox	**Nervous System**: Oligodendrocyte Precursor Cells
SOX6[5]	HMG/Sox	**Nervous System**: Adult Dopaminergic Neurons; Adult Oligodendrocyte Precursor Cells; Oligodendrocyte Precursor Cells
SOX9[2]	HMG/Sox	**Nervous System**: Late MN Progenitor Cells; d3, d4 and d5 Neural Progenitor Cells; Bergmann Glia; Adult Neural Stem Cells; Endothelial Cells; Oligodendrocyte Precursor Cells; **Eye**: Late Retinal Progenitor Cells; Mature Muller Glia Cells; Mature Retinal Pigmented Epithelium Cells;

ADNP[4]	Homeodomain	No differential expression during embryo stages
ARX[3]	Homeodomain	**Nervous System**: Floor Plate Cells Late Floor Plate Cells
DLX1[3]	Homeodomain	**Nervous System**: Lateral Ganglionic Eminence Progenitor Cells; Anterior Entopeduncular Progenitor Cells; Caudal Ganglionic Eminence Progenitor Cells; Medial Ganglionic Eminence Progenitor Cells; Endothelial Cells; Mesencephalic Neural Crest Cells; Cranial Neural Crest Cells;
DLX2[2,3]	Homeodomain	**Nervous System**: Lateral, Medial and Caudal Ganglionic Eminence Progenitor Cells; Anterior Entopeduncular Progenitor Cells; Mature Endothelial Cells; Endothelial Cells **Eye**: Mature Horizontal Cells; Dopaminergic Amacrine Cells; Dopaminergic Amacrine Cells; Mature Ganglion Cells;
DLX5[3,4]	Homeodomain	**Nervous System**: Mesencephalic Neural Crest Cells; Diencephalic Neural Crest Cells; Cranial Neural Crest Cells
DLX6[4]	Homeodomain	**Nervous System**: Cranial Neural Crest Cells
EN2[4]	Homeodomain	**Nervous System**: Fetal Dopaminergic Neurons; Myelinating Oligodendrocyte Cells; Dopaminergic Progenitor Cells; Early Floor Plate Cells; Meso-diencephalic Dopaminergic Precursor Cells; Hinge Point Cells; Isthmus Cells; Neural Fold Cells;
LHX2[2]	Homeodomain	**Nervous System**: Primitive Spinal Cord; Telencephalon; Mesencephalic Basal Plate; Diencephalon; Metencephalic Alar Plate; Metencephalic Basal Plate **Eye**: Late Retinal Progenitor Cells; Mature Muller Glia Cells; Early Retinal Progenitor Cells; Retinal Pigmented Epithelium Progenitor Cells;
LHX6[5]	Homeodomain	**Nervous System**: Medial Ganglionic Eminence Progenitor Cells**Cranial Neural Crest Cells**
NKX2.2[3]	Homeodomain	**Nervous System**: Myelinating Oligodendrocyte Cells; Late MN Progenitor Cells **; V3 Neural Progenitor Cells; Astrocyte Precursor Cells; Basal Plate Cells
PITX3[4]	Homeodomain	**Nervous System**: Dopaminergic Neurons **Eye**: Anterior Lens Epithelial Cells; Lens Vesicle Cells; Lens Placode Cells
RAX[3]	Homeodomain	**Nervous System**: Hypothalamus; Pituitary Gland; Thalamus; Pons **Eye**: Late Retinal Progenitor Cells; Mature Rod Cells; Muller Glia Precursor Cells; Early Retinal Progenitor Cells;
SHOX[4]	Homeodomain	No differential expression during embryo stages
SIX3[3]	Homeodomain	**Nervous System**: Anterior Neural Ridge Cells; Zona Limitans Intrathalamica Cells; Neural Fold Cells; Cranial Neural Plate Cells; Intraembryonic Neural Ectoderm Cells;
PAX6[3,4]	Homeodomain; Paired box	**Nervous System**: Lateral and Caudal Ganglionic Eminence Progenitor Cells; d3, d4 and d5 Neural Progenitor Cells; Mature Endothelial Cells; Endothelial Cells; Neocortical Radial Glia Cells; Early MN Progenitor Cells; VA1 and VA2 Fibrous Astrocyte Cells;

POU3F1[3]	Homeodomain; POU	No differential expression during embryo stages
POU3F2[5]	Homeodomain; POU	**Nervous System**: Pro-myelinating Schwann Cells**; Immature Schwann Cells
POU3F3[2]	Homeodomain; POU	**Nervous System**: Hypothalamus; Thalamus; Striatum; Medulla Oblongata; Cerebral Cortex; Midbrain tegmentum; Mesencephalic Ventricular Zone; Telencephalon; Diencephalic Ventricular Zone; Diencephalon; Metencephalic Alar Plate; Cerebellar Ventricular Zone Metencephalic Basal Plate
POU5F1[3]	Homeodomain; POU	No differential expression during embryo stages
HSF1[3]	HSF	No differential expression during embryo stages
MEF2C[6]	MADS box	**Nervous System**: Telencephalon; Metencephalic Alar Plate; Metencephalic Basal Plate
MECP2[2]	Methyl-CpG DNA-binding, AT-hook	No differential expression during embryo stages
NR2F2[2]	Nuclear receptor	No differential expression during embryo stages
RARB[4]	Nuclear receptor	No differential expression during embryo stages
RORγt[4]	Nuclear receptor	**Immune System**: Double Positive Thymocytes
PAX5[4]	Paired box	**Nervous System**: Metencephalic Alar Plate; Metencephalic Basal Plate **Immune System**: Small Pre B-Cells; Pro B-Cells; Large Pre B-Cells; Immature B-Cells
NF-Kb[3,4]	Rel	**Nervous System**: Medulla Oblongata; Metencephalic Basal Plate
STAT1[5]	STAT	**Nervous System**: Cerebral Cortex **Immune System**: T Helper Cells; T-Cytotoxic Cells
STAT3[3,4]	STAT	No differential expression during embryo stages
T-bet[4]	T-box	**Eye**: GABAergic Amacrine Cells
TBR1[3,4]	T-box	**Nervous System**: Hypothalamus; Thalamus Cerebral Cortex; Telencephalon; Diencephalon; Metencephalic Alar Plate

Table 2: Enriched pathways associated with the set of transcription factors described as altered in Section 2 – Genetic-associated neurodevelopmental disorders. All TFs described in this section were summarized and submitted to analysis in the Reactome® Software. The outcome demonstrated the most represented biological pathways associated with the specific group, suggesting important pathways that may be interfered by impairments in the TF (which do not exclude other pathways). The table is an adaptation of the complete map (Supplementary Figure 1). [1]Rett Syndrome; [2]Pitt Hopkins Syndrome; [3]SOX-associated disorders (Lamb-Shaffer Syndrome; Waardenburg–Hirschprung disease, campomelic dysplasia and Coffin-Siris Syndrome); [4]Williams Syndrome; [5]Dravet Syndrome.

Gene Transcription
Alteration in MECP2 binding processes to methylated DNA[1]; Regulation of MECP2 transcription and its activity on TF and pathways associated with GABAergic signaling[1]; FOXO-mediated transcription of cell cycle genes[1] Regulation of transcription mediated by RUNX1 AND 3 genes[3] Regulation of the transcription pathway associated with the YAP1 TF[4]; Regulation of transcription associated with the development of Treg lymphocytes[4].
Cell Cycle[5]
Cyclin D signaling[5]; Regulation of DNA duplication processes[5]; Regulation of G1 and G2 states and cellular differentiation processes[5].
WNT/β-catenin Pathway[2]
Developmental Biology Pathways[3]
Activation of HOX genes during differentiation[3] Schwann cell myelination[3]
NOTCH 3/4 signaling pathway[4]
Myogenesis[4]

Table 3: Enriched pathways associated with the set of transcription factors described as altered in Section 3 – Environmental factors and TFs in Psychiatric Disorders. All TF described in this section were summarized and submitted to analysis in the Reactome® Software. The outcome demonstrated the most represented biological pathways associated with the specific group, suggesting important pathways that may be interfered by impairments in the TF (which do not exclude other pathways). The table is an adaptation of the complete map (Supplementary Figure 2). The superscript numbers indicate overlaps of enriched pathways observed in this section with: [1]Genetic disorders; [2] Autism Spectrum Disorder, and [3]Schizophrenia.

Gene Transcription
Regulation of RNA polymerases I and II[1,2,3]; Regulation of siRNA and miRNA biogenesis; Regulation of transcription associated with RUNX 1 and 3 genes[1,2,3].
Cell Signaling
Autophagy; Establishment of senescence-associated secretory phenotype; Estrogen signaling; Leptin signaling[2,3]; NF-kb signaling[2]; NTRK signaling; Response to hypoxia; β-catenin deactivation[2,3]; Notch signaling
Development
Activation of HOX genes[1,2]; Adipocyte differentiation; Cell proliferation[2,3]; Granulopoiesis[3]; Maintenance of differentiation especially in the rhombencephalon[2]; Myogenesis[3]; Regulation of myelination in Schwann cells[1]; Stem cell differentiation[2,3].
Immune System

Control of inflammasome production[2];
Interferon Signaling[2,3];
Interleukin signaling (IL1[2], IL4[2], IL6[2,3], IL9[2,3], IL12[2,3], IL13[2,3], IL15[2,3], IL17[2], IL21[2], IL23[2,3], IL27[2,3], IL35[2,3])
MAPK activation[2];
Regulation of pathways associated with Toll-like 2, 3, 4, 5, 7, 8, 9 and 10 receptors.

Table 4: Enriched pathways associated with the set of transcription factors described as altered in Section 4.1 - Autism Spectrum Disorder (ASD) and TFs. The TFs described in this section were summarized and submitted to analysis in the Reactome® Software. The outcome demonstrated the most represented biological pathways associated with the specific group, suggesting important pathways that may be interfered by impairments in the TF (which do not exclude other pathways). The figure is an adaptation of the complete map (Supplementary Figure 3).

Gene Transcription
Epigenetic regulation of genetic transcription; Regulation of pathways associated with nuclear receptors; Regulation of RNA polymerases I and II; Regulation of transcription associated with MECP2; Regulation of transcription associated with RUNX 1, 2 and 3 TF and their impact on the WNT pathway.
Cell Signaling
Leptin signaling; NF-κb signaling; PDGF signaling; Tyrosine kinase receptor signaling; WNT / beta catenin signaling.
Development
Activation of HOX genes; Cell proliferation; Maintenance of differentiation especially in the rhombencephalon; Stem cell differentiation.
Immune System
Activation of chemokine production; Control of inflammasome production; Detection of pathogenic DNA and signal transduction; GM-CSF signaling; Interferon signaling; Interleukin signaling (IL1, IL3, IL4, IL5, IL6, IL9, IL12, IL13, IL15, IL17, IL21, IL23, IL27, IL35); MAPK activation.
Protein Metabolism
Activation of chaperones. Incretin signaling; Synthesis of peptide hormones.

Table 5: Enriched pathways associated with the set of transcription factors described as altered in Section 4.2 – Schizophrenia and TFs. The TFs described in this section were summarized and submitted to analysis in the Reactome® Software. The outcome demonstrated the most represented biological pathways associated with the specific group, suggesting important pathways that may be interfered by impairments in the TF (which do not exclude other pathways). The Table is an adaptation of the complete map (Supplementary Figure 4).

Gene Transcription
Epigenetic regulation of gene transcription; Regulation of RNA polymerases I and II; Regulation of transcription associated with MECP2; Regulation of transcription associated with RUNX 1, 2 and 3 genes.
Cell Signaling
Leptin signaling; PDGF Signaling; SCF/KIT Signaling; Tyrosine kinase receptor signaling; WNT/ β-catenin signaling; WNT-independent β-catenin pathways; β-catenin degradation complex.
Development
Cell proliferation; Granulopoiesis; Myogenesis; NODAL signaling; Stem cell differentiation.
Immune System
Growth hormone signaling; Interferon alpha, beta and gamma signaling; Interleukin signaling (IL2, IL4, IL6, IL9, IL12, IL13, IL15, IL20, IL23, IL27, IL35).

Graphical Abstract