Psychiatr. Pol. ONLINE FIRST Nr 378: 1–20
Published ahead of print 23 September 2025
www.psychiatriapolska.pl
ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
DOI: https://doi.org/10.12740/PP/OnlineFirst/208424

What do the GWAS studies say about language in schizophrenia?

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Summary

Aim. Schizophrenia links with altered language structure and may be evolutionary consequence of language development. High heritability of the disease led to recent endeavour in explaining the genetic background. Genome-Wide Association Studies (GWAS) indicate schizophrenia as highly polygenic disease with many receptor and synaptic plasticity pathways engaged.

Material and methods. Here we present a systematic review on the topic of schizophrenia GWAS findings and its potential relevance to language skills. We used GWAS catalogue data to identify all significant associations in schizophrenia (including selected endophenotypes) and studied its relevance in the context of language phenotypes associations.

Results. Among genes involved in language evolution, *FOXP1* and *ROBO2* were indicated by GWAS as associated with schizophrenia. Evidence on schizophrenia linked SNPs was found for association with intelligence, educational attainment, cognitive abilities, and language processing brain structures imaging results.

Conclusions. The review discusses hypotheses of language alterations in schizophrenia as a consequence of impaired synaptic plasticity and neural network formation.

Key words: genetics, schizophrenia, language

Introduction

Genome-wide association studies (GWAS) are often used to study the molecular basis of schizophrenia [1]. The core benefit of GWAS is that it enables a wide platform examination of single-nucleotide polymorphisms (SNPs) genetic variants in affected and control subjects, as well as searching for biological associations without hypoth-

esised target. Stringent statistical rules are employed to find evidence of associations between clinical phenotypes and SNPs in studied individuals.

At the time of writing (April 2023), the GWAS catalogue (https://www.ebi.ac.uk/gwas/home) featured over 471,482 associations across near six thousand research papers. Horwitz et al. [2] found that 6,632 SNPs were associated with psychiatric symptoms, with 1,109 reaching the genome-wide statistical significance (as at 2017).

The main challenge of GWAS in schizophrenia is the sample size required to empower reaching the genome-wide significance and phenotypic heterogeneity of the studied population. Hence, the most reliable data usually comes from multi-centred collaborations. The largest study to date [3] revealed 287 valid, independent loci in the sample size of 76,755 patients and 243,649 healthy controls. Most reliable findings indicated molecular pathways crucial for schizophrenia, like GABA-ergic, dopaminergic and glutamatergic signalling (*GRIN2A*), calcium signalling (*CACNA1C*), as well as major histocompatibility complex (*MHC* [4] and *FOXP1* [3]) associations. Overall, it is estimated that current data can explain over 30% of schizophrenia heritability, although gaps exist in understanding the realm of epigenetic and evolutionary aspects in populations of different ancestry [5].

It is hypothesized that the first-rank symptoms of schizophrenia such as thought steering, auditory verbal hallucinations (AVH) and formal thought disorders (FTDs) can have a common background of language disturbance. This phenomenon is complex and can be explained by connectomics, molecular biology, as well as societal and cultural factors [6].

Language disturbance is recognised in many psychometric scales [7], such as the *Positive and Negative Symptoms Scale* (PANSS) [8], *Scale for the Assessment of Positive/Negative Symptoms* (SAPS, SANS), *Brief Psychiatric Rating Scale* (BPRS), *Thought and Language Index* (TLI) [9] or the *Operational Criteria Checklist for Psychotic Illness and Affective Illness* (OPCRIT) [10]. The presence of language disturbance symptoms affects the general prognosis of schizophrenic patients. Formal thought disorders (FTDs) are associated with poor social, occupational and neurocognitive functioning, as well as with a higher relapse rate [7]. FTDs are also linked with the phenomenological concept of the self, which may coincide with negative symptoms severity and cognitive deficits [11]. Auditory verbal hallucinations (AVH), seen in 60–70% [12] of patients, may not respond entirely to pharmacological management [12] and could be a risk factor for suicide and violent behaviour [13].

The language symptoms of schizophrenia can also be studied in an evolutionary context. Schizophrenia can be dated back to the language ability formation in our ancestors [14]. In this approach, Crow [15] recognises schizophrenia as the evolutionary consequence of language invention (the price that Homo sapiens pay for language. The language of the human species could have spawned as a genetic mutation, or co-evolved with social skills, shared intentionality or reasoning abilities [16]. Following Enard's approach [16] (2016), human speech may be an elaborated form of vocalisation, which is observed in other species, like birds or mice. Hence, translational genetic studies may reveal specific genetic variants that occurred in human evolution resulting in human language acquisition. The main restriction of translational studies

between human and other species relies on similarity between animals' vocalisations and human language which is not obvious.

Until today, translational studies have identified putative language-related genes such as *FOXP1* and *FOXP2, CNTNAP2, ROBO1* and *ROBO2, KIAA0319, GNPTAB, GNPTG, SRPX2, ATP2C2, DCDC2, CMIP, DYX1C1, TSC1, NFXL1*, and *NAGPA* [16–18]. However the biology of human language may significantly differ from this known in other species.

Linguistic assessment can also be a valuable clinical tool in schizophrenia diagnosis and screening for at-risk mental states. Quantitative analysis of speech samples can distinguish individuals with schizophrenia from healthy controls by assessing linguistic abilities [19]. This observations are reflected in functional brain imaging results, which show aberrant connectivity in auditory and language brain networks [20].

In this review, we present the data from GWAS studies, available in the GWAS catalogue (as at February 2023). The study aim was to seek for common genes proven in GWAS as significant for schizophrenia and involved in language ability formation.

1. Materials and Methods

We searched the GWAS catalogue (https://www.ebi.ac.uk/gwas/) using the query 'schizophrenia' (131 articles, number of associations obtained: $n = 6953$). Then, we scanned each title and abstract for eligibility. We excluded studies conducted on mixed-diagnosis populations (e.g. schizophrenia + bipolar disorder or autism) and non-schizophrenia populations (38 publications, $n = 2326$ associations), studies assessing associations between SNPs and the drug response, eye-movement dysfunctions, aggression and violence, smoking behaviour, diabetes risk, interaction with cytomegalovirus infection, alcohol dependence or niacin metabolism (endophenotypes non-assessed for eligibility, 22 publications, $n = 431$); as not connected with language skills.

The following endophenotypes were included to the analysis: treatment-resistance [21, 22], neuroimaging studies [23–26], age at onset [27–29], neurocognitive functions [30, 31], neurophysiology of brain cortex [32], and schizophrenia symptomatology [33–35]. Next, we made a list of each SNP indicated in a GWAS study and we assessed the association significance according to the GWAS threshold. We removed all non-significant associations and duplications ($p > 10^{-8}$; $n = 2512$).

Overall, 1684 associations localised in 748 genes and 476 intergenic regions were found as significant (see supplementary materials). Each of the listed SNPs was subsequently searched using the GWAS catalogue to find if it is associated with language symptoms in the database. Then each gene was scanned if it is linked with language abilities [30].

Moreover, the list of genes perceived as evolutionarily involved in language development (the genes mentioned above, see: [17]) was compared to SNPs and genes significant in GWAS for schizophrenia and its selected endophenotypes. A detailed process of data selection is available in the diagram (Figure 1). Detailed list of genes included in analysis (significantly associated to schizophrenia) is attached in a supplementary file. We used *Annotation, Visualisation and Integrated Discovery Clas-*

sification System (DAVID 6.8) [36] to identify biological pathways associated with selected genes.

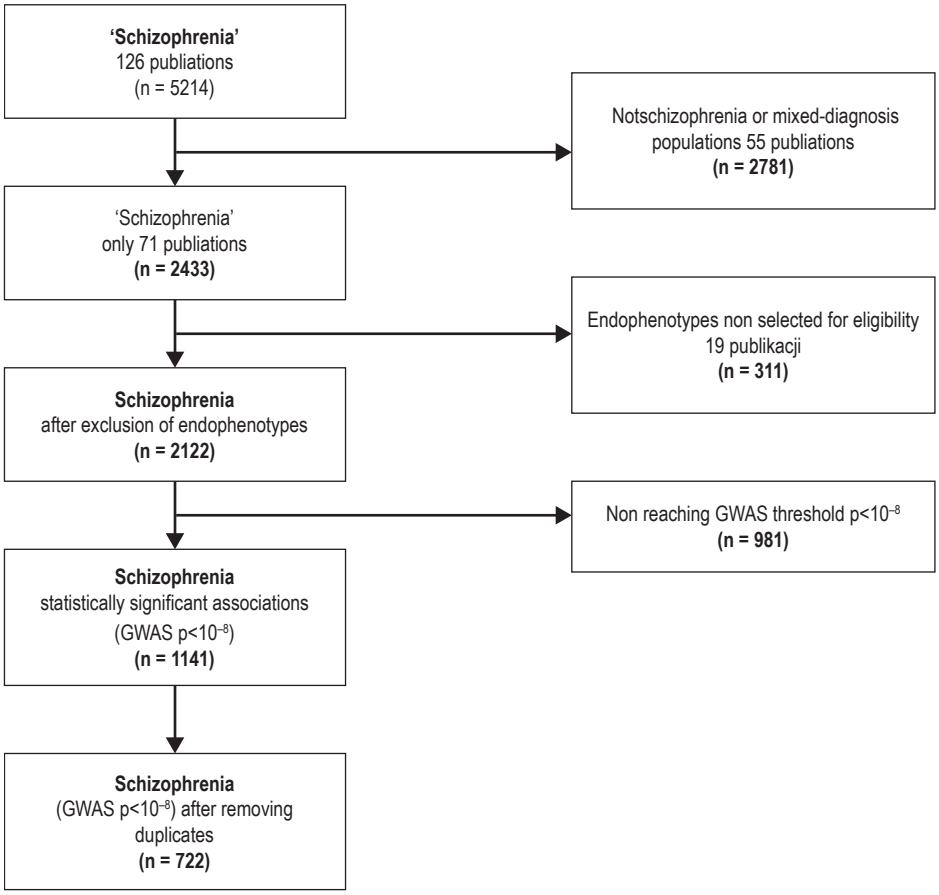

Figure 1. **The process of data selection in the GWAS catalogue**

2. Results

Among the genes influencing the acquisition of language skills in the light of the evolutionary approach, only the *FOXP1* and *ROBO2* genes are indicated as being associated with schizophrenia [30].

We did not find any significant GWAS results in schizophrenia on majority of putative language genes (see *Introduction* and [17]): *FOXP2, CNTNAP2, ROBO1, KIAA0319, GNPTAB, GNPTG, SRPX2, DCDC2, CMIP, DYX1C1, ATP2C2*, and *NAGPA*. Comparing abovementioned list to genes associated with schizophrenia diagnosis, *FOXP1* and *ROBO2* genes only are involved. Study by Lam et al. [30] (2019) revealed

association of two SNPs, in *FOXP1* (rs62244881, 3p12.3) and *ROBO2* (rs3849490, 3p12.3), with schizophrenia.

We did not find any direct associations between GWAS-significant SNPs for schizophrenia and selected endophenotypes and direct language traits in GWAS catalogue. Evidence of selected SNPs associations was found for intelligence, educational attainment and cognitive abilities. Several SNPs were also associated with brain volume imaging, including language functional connectivity. Below, SNPs significantly associated with schizophrenia and its selected endophenotypes are enumerated in the context of traits indirectly linked to language skills. Four, independent studies [37–40] showed 9 SNPs found in schizophrenia studies as related to intelligence. The SNPs are located in 9 gene areas: *SEPTIN3* [39]*, LINC00461* [40]*, CALN1, PRKD1, CARMIL1-CMAHP, RPS19BD1-CACNA1I, OR2U2D-OR14J1, PTPNR2* [38], and *RAI1* [37]. Educational attainment was associated with 19 gene areas [30–41]: *DPYD, NFIA, CORO1C, VWA52B, BCL11B-SETD3, ZSWIM6, GGNBP1*[41], *PALS2, BNIP3L, GLCCI1* [39], *TAOK2, TCF4, EP300-AS1, ZEB2, ATP2A2, FURIN* [30], *CEP57-MTMR2* [42]*, KCNG2-CTDP1* [43]*, PCGEM1-SLC44A3P1* [39–42]. Regarding the association with cognitive abilities two independent studies [37, 39] and a meta-analysis [30] indicated 25 SNPs, located in 21 identified genes (2 SNPs for *TSNARE1*, 3 SNPs did not map to the genome). For rs13107325 (*SLC9A8*, 4q24) significant associations were obtained in brain imaging: volumetrics of subcortical nuclei, cerebellum and brain stem, as well as cortical thickness in general, including temporal lobe [44–47]. For rs160593 (*LIN28B*, 6q21) association was found for cortical surface area [48]; rs245201 (*CCDC192*, 5q23.2) was associated with functional imaging of dorsolateral prefrontal cortex (dlPFC) [49]. Particular significance for language was found for rs4702 (*FURIN*, 15q26.1), rs62266110 (*HSPE1P19-RNU6448P,* 3q11.2) and rs35124509 (*EPHA3,* 3p11.1), which were associated with resting-state functional connectivity of brain language areas [50].

Out of 748 genes associated with schizophrenia, 263 genes were found to be associated with educational attainment as well, 193 with cognitive ability, 133 with intelligence, and 342 with brain imaging data. Associations with more specific language traits were observed for 24 genes. These genes, including their chromosomal location, function and evidenced association with language are presented in Table 1.

Table 1. **Loci identified in schizophrenia GWAS studies, associated with language features, based on GWAS Catalogue (https://www.ebi.ac.uk/gwas/home; retrieved: April 2023)**

Gene	Chromosomal location	Function	Language parameter	Citation
ACTG1P22	2p16.1	Actin gamma-1 pseudogene 22	Language network functional connectivity	Mekki Y et al., 2022 [50]
AXDND1	1q25.2	Axonemal dynein light chain domain containing 1	Stuttering	Shaw DM et al., 2021 [53]
CACNA1C	12p13.33	Calcium voltage-gated channel Subunit 1 c	Short-term verbal memory	Gialluisi A et al., 2019 [96]

table continued on the next page

CALN1	7q11.22	Calneuron 1	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
ETF1	5q31.2	Eukaryotic translation termination Factor 1	Verbal test score	Greenwood TA et al., 2019 [97]
FOXO3	6q21	Forkhead box O3	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
LINC01435	10q25.1	Long intergenic non-protein Coding rna 1435	Cognitive language assessment	Homann J et al., 2022 [58]
LINC02404	12q21.33	Long intergenic non-protein Coding rna 2404	Stuttering	Shaw DM et al., 2021 [53]
LPP	3q28	LIM domain containing preferred translocation partner in lipoma	Verbal memory	Arpawong TE et al., 2017 [98]
MAGI2	7q21.11	Membrane-associated guanylate kinase, WW and PDZ domain containing 2	Reading ability	Davis OS et al., 2014 [56]
MIR124-2HG	8q12.3	MIR124-2 host gene	Verbal memory	Debette S et al., 2014 [100]
PHACTR3	20q13.32	Phosphatase and actin regulator 3	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
SGCZ	8p22	Sarcoglycan zeta	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
TCF20	22q13.2	Transcription factor 20	Language ability	Homann J et al., 2022 [58]
LCORL	4p15.31	Ligand-dependent nuclear receptor corepressor	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
NEGR1	1p31.1	Neuronal growth regulator 1	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
SEPTIN3	22q13.2	Septin 3	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
ARL14EP-DT	11p14.1	ARL14EP divergent transcript	Dyslexia	Doust C et al., 2022 [54]

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ITIH1	3p21.1	Inter-alpha-trypsin inhibitor heavy chain H1	Verbal learning	Lahti J et al., 2022 [59]
GLI3	7p14.1	Zinc finger protein GLI3	Verbal functions in elderly	Deters KD et al., 2017 [57]

2.1. Verbal memory

Verbal memory comprises encoding, storage and retrieval of the verbal material, including immediate or delayed recall. A literature review revealed three genes sharing a potential common impact on schizophrenia and verbal memory. A study by Gialluisi et al. [96] encompassed GWAS of children population with developmental dyslexia (DD) and indicated two potential candidate genes: *MIR924HG* and *NKAIN3*; *CACNA1C*, rs11062222 SNP did not obtain the GWAS *p* threshold ($p > 10^{-6}$). Further two studies assessed the genetic associations of age-related verbal memory decline in the elderly-adult population.

In the work by Arpawong et al. [98], genome-wide significance was obtained for *TOMM40* and *APOE* SNPs and delayed verbal recall testing, another *APOE* SNP was also identified by Debette et al. as associated with the delayed recall [100]. To sum up, SNPs identified in schizophrenia cohorts did not meet the GWAS statistical threshold in studies on verbal memory.

2.2. Verbal numerical reasoning

Verbal numerical reasoning (VNR) has been recently indicated as strongly related to schizophrenia genetic background. A combined analysis by Smeland et al. [51] (2017) indicated two loci associated with VNR and schizophrenia: *TCF20* (22q13.2) and SLC39A8 (4q24).

Furthermore, the analysis by de la Funete et al. [52] (2021) identified 7 loci associated both with schizophrenia and VNR: *LCORL* (4p15.31)*, NEGR1* (1p31.1), *CALN1* (7q11.22), *FOXO3* (6q21), *PHACTR3* (20q13.22), and *SGCZ* (8p22), *SEPTIN3* (22q13.2*)*, all of SNPs meet the threshold of GWAS significance ($p < 10^{-8}$).

2.3. Stuttering

We found one GWAS by Shaw et al. [53] (2021) showing potential shared genetic evidence on schizophrenia and stuttering, with two loci: *AXDND1* (1q25.2) and *LINC02404* (12q21.33). The second one met the GWAS threshold of significance at rs115024493.

2.4. Dyslexia

Dyslexia is pervasive neurodevelopmental disorder with reading and linguistic disturbances. In two independent GWAS studies [54, 55] three of genes significant for schizophrenia were found: *EPHA4, ARL14EP-DT, HTT*. *ARL14EP-DT* gene (11p14.1) SNPs met the statistical threshold in GWAS study that assessed 51,800 subjects with dyslexia and over one million healthy controls [54].

2.5. Other findings

ACTG1P22 identified in schizophrenia GWAS was significantly linked with language functional disconnectivity in the study by Mekki et al. [50]. Two other genes were linked with reading ability in children (*MAGI2*) [56] and two with language ability (*TCF20, GLI3*) in individuals with Alzheimer's disease [57, 58]. *GLI3* SNP (rs3801203) met statistical threshold for GWAS significance. For verbal learning, study by Lahti et al. [59] identified two genes previously found as significant for schizophrenia (*ITIH1, PRKAG2*). For *ITIH1* (3p21.1), three SNPs met GWAS statistical significance (rs2239551, rs2286798, rs678).

Pathway analysis by *Database for Annotation, Visualisation and Integrated Discovery Classification System* (DAVID 6.8) [36] revealed engagement of significant genes in two categories with potential impact on central nervous system: nerve growth factors response and cellular homeostasis (for details see supplementary data: DAVID).

3. Discussion

Despite strong suggestions of the genetic background of language ability in humans, current evidence stemming from GWAS studies did not show any clear genetic architecture of language. From the analysis of the literature we performed, the linguistic background of schizophrenia appears to be complex and polygenic. Out of 14 identified genes, 10 are known as protein-coding and may be functionally classified as: calcium signalling molecules (*CACNA1C, CALN1*), transcription factors (*ETF1, FOXO3, TCF20*) and cytoskeleton-cell adhesion molecules (*AXDND1, LPP, SGCZ, PHACTR3*, and *MAGI2*). Engagement of these three groups of biological factors suggests the common denominator of language disturbances as the consequence of synaptic plasticity and neural network formation impairment.

3.1. Transcription factors and language

The role of transcription factors in language disturbances is exerted by the family of forkhead box/winged-helix (FOX) proteins [60]. The FOX family of proteins contains a highly conserved DNA-binding domain (forkhead domain) and serves as transcription factors in processes of cell differentiation, expression of genes and metabolic coordination [60]. In the human genome, 17 classes of fox proteins (fox: A to Q) were classified with localisation proneness to centromeric and telomeric parts of chromosomes [61].

Until today, the main candidate gene for linguistic skills and disturbances is seen in *FOXP2*. The transcription factor *FOXP2* interacts with multiple gene promoters, including *CNTNAP2* or *DISC1* and has been linked with developmental speech apraxia (DAS) and speech-language disorder (*SPCH1*) [62], moreover, rs10447760 SNP was associated in genetic studies on the Chinese population with schizophrenia [63]. *FOXP2* expression change is therefore suggested as the evolutionary switch in modern human development leading to language exuberance. However, we did not find direct evidence in GWAS studies for an association of *FOXP2* with schizophrenia.

Another important gene is *FOXO3*. It appears that in schizophrenia, mutations in this gene cause disruption of the forkhead box protein pathway. The *FOXO3* gene encodes the Fox-O3 transcription factor, expressed ubiquitously and related to the processes of ageing [64]. Due to its structure, it is involved in the cell's response to oxidative stress, apoptosis, cell cycle regulation, as well as in the response to insulin and insulin-like growth factor 1 (*IGF-1*). Studies on *PC12* (pheochromocytoma-derived) cells revealed the impact of clozapine treatment on the phosphorylation status of Fox-O3 proteins and potential corticosteroids stress response [65], hence atypical neuroleptic action may promote defence mechanisms in neural cells, by inhibiting the impact of ageing and stress. Another analysis connects *FOXO3* with brain volume. A study by Smeland et al. [66], on a large group of patients (n = 82,315), identified a polymorphism within *FOXO3* (rs10457180) associated with smaller brain volume. This suggests a similar process to that seen in dementia, which leads to a systematic reduction in brain volume. Among schizophrenia patients, the expression of Fox-O3 mRNA was also recently found to be altered and related to olanzapine treatment [67].

Another significant gene found in schizophrenia GWAS studies was *FOXP1*, engaged in brain development [68]. The *FOXP1* encodes forkhead box protein 1 transcription factor; mutations in this gene was identified as the cause of *FOXP1* syndrome (*FOXP1S*) linked with intellectual disability and language delay combined with autism spectrum [68].

The abovementioned evidence suggests possible impairments in molecular DNA repair mechanisms, which may be related to brain aging processes [69].

3.2. Calcium signalling and language

The role of calcium ions is stressed by their engagement in the action of G protein-coupled receptors (*GPCR*) crucial for the central nervous system and serves as a therapeutic target in schizophrenia [70]. Calcium signalling also provides excitatory-inhibitory balance in neural networks due to GABA/glutamate interaction and generating the proper oscillatory rhythm [71]. Here we put forward two potential genes, encoding calcium-related proteins as playing the role in schizophrenia and language.

The first gene – *CACNA1C*, encoding calcium voltage-gated channel subunit alpha1 (Cav1.2), has been recognised in genetic association studies as related to schizophrenia, major depressive disorder and autism [72].

The Cav1.2 forms a pore through which calcium flows into the cell and initiates further signalling cascades regulating gene expression – these involve cAMP response

element binding protein (CREB) and Ca2+/calmodulin-dependent protein kinase (CaMKII). This pathway is believed to be essential for maintaining long-term neural plasticity mechanisms. This pathway is believed to be essential for maintaining long-term neural plasticity mechanisms. A recent study by Rodan et al. [73] described the *CACNA1C* variant as determining neurodevelopmental delay phenotype combined with expressive language dysfunctions. Hence, language decline seems to be the trait depending on global disruption of brain development, impacting motoric ability, epileptogenesis and autism traits. The broader clinical picture of *CACNA1C*-derived genetic syndrome is recognised as the autosomal dominant Timothy Syndrome defined by QT interval prolongation and subsequent cardiac dysrhythmias, syndactyly and facial dysmorphic features [74].

The second finding, *CALN1* is a protein-coding gene localised on 7q11.22, widely expressed in the central nervous system; the encoded product, calneuron 1 protein, is thought to be engaged in learning processes [75]. The detailed, molecular role of calneuron 1 is not fully understood. It is believed that the protein regulates vesicular transport as a part of the trans-Golgi network [76].

3.3. Neural cells adhesion and language

Here, we identified five genes taking part both in schizophrenia and language disturbances which may be collectively classified as cell adhesion/cytoskeleton. Engagement of this gene group suggests common background based on intracellular and intercellular mechanisms of connection shaping and plasticity in neural networks. The key role in the disruption of these cellular mechanisms is played by the *DISC1* protein, which occurs in rare cases of hereditary mental illnesses [77]. The Disc1 protein serves as a metabolic hub, integrating cell membrane signalling, second messengers and cytoskeleton in processes of neuronal migration and neurogenesis (particularly in embryonal development) and synaptic plasticity (also in adulthood). It has been suggested that mutation of the *DISC1* gene causes impaired cAMP signalling and increased activity of phosphodiesterase 4 [78], impaired neuronal branching due to dynein motor complex interaction [79] and aggregation of Disc1 protein multimers among neural cells [77], which results in the occurrence of psychiatric symptoms.

A similar association with the cytoskeleton is seen for *AXDND1* and *SGCZ* gene indicated in the review, encoding axonemal dynein light chain and zeta-sarcoglycan domain. *AXDND1* has been recently recognised as crucial for cytoskeleton motility in sperm cells [80], the *AXDND1* mRNA is expressed in the brain [81], however, the putative role in neuronal cytoskeleton has not been confirmed. In the case of zeta-sarcoglycan, the molecule is engaged in the dystrophin-associated complex, clinically linked with muscular dystrophies [82].

Another mentioned gene, *PHACTR3*, plays similar cellular roles and was combined with the functioning of the central nervous system, including the prefrontal cortex structure [83]. Protein phosphatase and actin regulator 3 (phactr) molecules share a unique structure containing two motifs: G-acting binding protein and phosphatase-binding domain [84]; for the phactr3 (scapinin), studies on animal models confirm

its impact on axonal and dendritic length [84]. The impact of scapinin on neural cell morphogenesis may be associated with its forced activity near the cell membrane [85]. Cell membrane activity also links with the *MAGI2* gene product (membrane-associated guanylate kinase), engaged in AMPA receptors (*AMPAR*) synaptic trafficking and recently linked with neurodevelopmental disorder and epilepsy [86].

In summary, indicated genes take part in neurodevelopment, cell and connection shaping, as well as migration. The potential implication to language processing may be explained by a global impairment of neural network shaping on the interhemispheric level, organisation of language centres in the brain, and finally local anatomic changes due to impaired connectivity [87].

4. Summing-up previous GWAS data and recent genome mapping in the context of language

Recent results by Trubetskoy et al. [3] strongly underline the role of pre – and postsynaptic molecular pathways, previously identified as common in neurodevelopmental disorders including autism-spectrum disorder (ASD) [88]. These pathways include excitatory-inhibitory balance in neural networks. Genetic studies indicate schizophrenia as having high overlap with neurodevelopmental speech disorders and autism due to glutamatergic system impairment [89].

The common phenomenon, linking glutamate alterations in neurodevelopment with language features is disconnectivity. Altered functional connections were found in schizophrenia patients including language brain centres (e.g. Broca's area) and linked with synaptic plasticity deficits. These features may also progress with the course of the illness [90, 91].

Language disturbances, may be therefore a consequence of GABA – glutamate disequilibrium. Hence, overactive and prone to degeneration cortical neurons with concurrent GABA-interneuron hypofunction lead to diminished ability to form neural connections [92]. Disconnectivity seems to be a shared mechanism involved in general cognitive decline in schizophrenia. From this point of view, language symptoms reflect only neural associational alterations and do not emerge as an isolated pathology. GWAS studies show the association of schizophrenia diagnosis with major histocompatibility complex (MHC) genes and immunological factors (e.g. CD4) [3, 4, 93].

Chronic mild inflammation linked to schizophrenia is proposed as causal pathology for negative symptoms. Meta-analysis by Dunleavy et al. [94] (2022) suggests proinflammatory cytokines to be dysregulated in schizophrenia with an impact on negative symptoms spectrum. Regarding language, negative formal thought disorders (nFTD) may be a consequence of inflammatory neurodegeneration. Immunological approach should be interpreted having in mind restrictions due to MHC high linkage-disequilibrium [3]. In addition, other hypotheses should be considered, including disturbances of dopamine neurotransmission in the prefrontal cortex (PFC) [99].

5. Conclusion remarks and limitations

Based on the analysis of available GWAS studies, we have proposed several observations regarding the potential biological basis of language impairments in schizophrenia.

First, the polygenic structure of schizophrenia suggests that language impairments may arise from the interaction of multiple molecular pathways rather than a single genetic variant.

We identified several key mechanisms potentially linked to these impairments, including calcium signalling, morphogenesis and cell adhesion, and gene expression regulation (transcription factors) (Figure 2). Their influence on the central nervous system may be significant, but a full explanation requires further research.

Synaptic plasticity alterations may play a role in the language impairments observed in schizophrenia. However, the complexity of this process indicates that language-related symptoms of the disorder may result from the interplay of multiple factors, both biological and environmental. It is also important to consider other possible explanations, including psychological and social factors, which may impact language development and its impairments in schizophrenia.

Our study is not without limitations:

– We did not conduct our own raw data analyses, relying solely on available GWAS study findings.

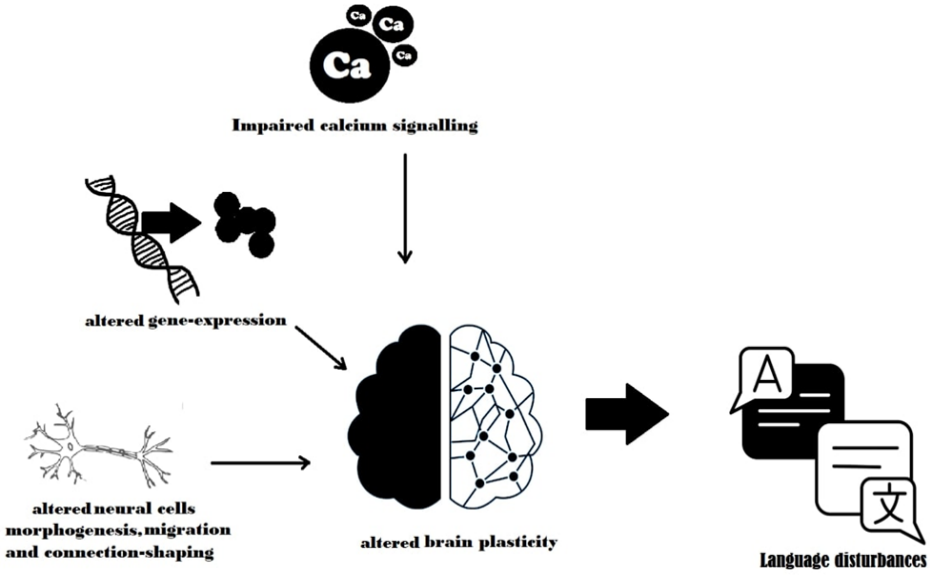

Figure 2. **Suggested mechanism of language impairment in schizophrenia**

- The gene regions identified as potentially associated with language and schizophrenia require further investigation to confirm their actual role.
- There is a lack of large genetic studies specifically focused on language, and the limited number of associations exceeding the GWAS significance threshold reduces the overall scientific value of the analysis.
- GWAS findings are based on correlations, meaning they do not establish a causal relationship. Despite genetic predispositions, the phenotypic expression of language-related traits in schizophrenia may be shaped by additional factors, such as environment and individual experiences [95].

In summary, the genetic determinants of language impairments in schizophrenia should be complemented with psychological and social perspectives to better reflect the multidimensional nature of the disorder

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