

Neurobiological etiology of impulsivity in the context of aggressive behaviors in schizophrenia

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Summary

The main aim of the article was to show the importance of impulsivity as a background to aggressive behavior displayed by people on the schizophrenia spectrum with particular attention to its biological determinants, including genetic ones. Imaging tests of the central nervous system allow for locating the centers responsible for particular types of impulsiveness and for modulating impulsive reactions. Excessive impulsivity may be attributed to disturbances in serotonergic, dopaminergic, and noradrenergic neurotransmission, as well as disrupted functioning of other neurochemical pathways due to genetic alterations (*COMT*, Ala72Ser, Val158Met, C957T, SLC6A4). Features indicating genetic diversity have been observed among people showing different forms of increased impulsiveness: motor, cognitive and lack of planning, which can be explained at the molecular level. Predicted to be among genes that predispose to mental and neurodevelopmental disorders accompanied by intense impulsiveness contributing to aggressive behavior include neuroligins and neurexins. The basis for such hypotheses is provided by the results of analyses conducted on animal models. It should be assumed that the results of further genetic tests in this area will allow for a more precise determination of the risk of aggression from perpetrators with psychotic disorders. This will lead to development of more effective and individualized therapeutic programs aimed at reducing the risk of dangerous behavior in this group of offenders, more efficient implementation of protective measures, and thus reduce costs of psychiatric treatment of insane perpetrators of prohibited acts.

Key words: impulsiveness, aggressive behaviors, schizophrenia

Introduction

Violence is one of major problems of the modern world and affects numerous spheres of human life. The European Psychiatric Association guidelines indicate that striving to minimize the risk of violent behavior is one of the important tasks of psychiatry, especially its subdiscipline – forensic psychiatry [1]. Compared to the

population of healthy people, the risk of aggressive behavior increases significantly in the group of people showing symptoms of schizophrenia [2], using psychoactive substances or manifesting personality disorders [3]. Some people diagnosed with schizophrenia commit illegal acts even before the first psychotic episode [4], which indicates the need to look for other causes of aggressive behavior than those resulting from the presence of symptoms of the disease. Assuming that the risk of aggression among these people results solely from the presence of psychotic symptoms, such as delusions or hallucinations, is an excessive simplification. Aggression in this group may also be caused by specific premorbid personality traits, cognitive deficits, impaired social functioning [5], as well as an increased level of impulsiveness [2, 6], which negatively affects quality of life factors for people on the schizophrenia spectrum, making it difficult for them to function socially without conflict (at the same time, the reverse relationship cannot be ruled out either) [7]. Furthermore, poor impulsivity control is a significant predictor of potential physical aggression in the long term in people with schizophrenia, in addition to substance abuse, non-compliance with medical advice, psychotic symptoms, mood disorder symptoms and poor support in the family environment [8]. This is particularly relevant in the case of insane offenders serving a protective measure.

There are also other opinions to the effect that among people with schizophrenia, impulsivity (especially behavioral impulsivity) treated as a permanent personality disposition contributes to aggressive behavior, especially with the co-occurrence of aggression as a personality trait, productive symptoms and taking into account environmental factors interfering with the functioning of such a person [9]. This extensive consideration of the etiology of aggressive behavior confirms the need to continue the search for predictors of aggression in schizophrenia spectrum patients that could be used to more accurately predict the risk of aggressive behavior.

The aim of the study and the method of the literature review

The aim of the narrative literature review was to analyze the biological factors that are identified as possible underlying impulsivity contributing to the aggressive behavior displayed by people on the schizophrenia spectrum: structural changes in the central nervous system, neurotransmitter dysfunction, and genetic conditions. It should be anticipated that future research findings in this area will be a valuable addition to psychological models of impulsivity.

For this purpose, online databases (mainly PubMed, to a lesser extent Polish bibliographic databases of scientific journals) were searched from January to July 2024 for relevant original and review articles. They used a combination of the following keywords: schizophrenia, impulsivity, aggressive behavior, magnetic resonance imaging, computer tomography, neurotransmitters, genetic factors, neuroligins, neurexins. Finally, 63 papers in Polish and English published up to 2024 were included in the review.

Impulsiveness

Impulsiveness is sometimes treated as a specific personality trait or an isolated behavior undertaken under the influence of a changed emotional state, which occurs not only in the course of various mental disorders, but also in particularly stressful situations or under the influence of the use of psychoactive substances [10]. Among psychological models of impulsiveness, the most important is Hans Eysenck's hierarchical theory, which focuses on the importance of balance between the inhibitory functions of cortical centers and excitations coming from the ascending reticular system (extraversion) and the limbic system (neuroticism) [10]. In the original version of this theory, impulsiveness was an element of extraversion, later it was included in a newly introduced personality dimension – psychoticism, which correlates with a high level of neuroticism and extraversion [11].

According to Moeller et al. [12], impulsive behavior is an expression of an individual's predisposition to quick, unplanned reactions in response to external and internal stimuli, without paying attention to potential negative consequences of such action. They are so fast that it is impossible to verify its consequences. One cause of impulsiveness may be a person's inability to accurately assess the benefits of delaying significant gratification versus a small but immediate reward. According to the authors, elements that should be included in every concept of impulsiveness are low sensitivity to possible negative consequences of one's own behavior, sudden and unplanned reactions that begin before the stimulus analysis is completed, and ignoring long-term consequences of one's own behavior [12].

Barratt distinguishes three forms of impulsiveness: (1) motor impulsiveness, reflected in, for example, acting without thinking, (2) cognitive impulsiveness, expressed, among others, in quick decision making, and (3) impulsiveness resulting from lack of planning and not thinking about the future [as cited in: 13]. Motor (behavioral) impulsiveness can therefore be interpreted as an inability to control the response to a stimulus, and cognitive impulsiveness as an inability to correctly assess consequences of current or future events and actions [14]. In other words, in the case of behavioral impulsiveness we can talk about impulsive action, while in the case of cognitive impulsiveness we can talk about impulsive choice [15]. It was found that people in the second category of impulsiveness are characterized by impairment of working memory and attention functions [16].

Changes in the central nervous system structures

Aggressive behavior can be treated not only as a consequence of impulsiveness, but also as a kind of its continuum [17]. However, there are reports questioning the importance of impulsiveness in generating aggressive behavior exhibited by people with schizophrenia [18], but at the same time its important role in this group of people is indicated [19]. In this context, research on the basis of neuropsychological deficits becomes important: centers located in the ventromedial prefrontal cortex are responsible for cognitive impulsiveness, and the dorsolateral areas of the prefrontal cortex

are responsible for behavioral impulsiveness [20]. The structures of the striatum, the limbic system, and the subthalamic nucleus are responsible for individual components of impulsiveness, which include initiating behavior, analyzing stimuli, and taking action appropriate to external stimuli [21, 22]. The centers modulating impulsiveness include the caudate nucleus, which determines the action process in time, and the locus coeruleus, which is associated with regulation of inhibition of functions of the frontal cortex [23, 24]. This is particularly important in the case of patients with schizophrenia spectrum, who are characterized by significant problems in the ability to inhibit strong responses to a stimulus [25]. Such people are characterized by an irresistible desire for immediate gratification with a less valuable reward compared to delayed but greater gratification, which is interpreted as a narrowed ability to evaluate incoming information [26].

Hoptman et al. [27] found that patients with schizophrenia with an increased level of impulsiveness compared to healthy people have reduced cortical thickness in the ventral prefrontal areas, as well as weakened functional connectivity between the ventral prefrontal and limbic areas. Imaging studies also indicate the importance of abnormalities in circuits involving the medial temporal regions as playing an important role in impulsivity and aggressive behavior in schizophrenia [6].

Another study revealed that reduced activation of the medial prefrontal cortex characterized people with schizophrenia who impulsively attempted suicide [28]. The research by Tikász et al. [29] indicated that in patients with schizophrenia exhibiting aggressive behaviors, there was reduced activation of the dorsolateral prefrontal cortex, suggesting diminished ability to inhibit emotional reactions through cognitive functions.

A multicenter study (2,095 people with a diagnosis of schizophrenia) using MRI findings revealed that aggressive behavior in this group was significantly related to changes in the central nervous system: decreased total cortical volume, decreased global white matter integrity, decreased dorsolateral prefrontal cortex volume, decreased inferior parietal lobe volume and inner pouch integrity. These changes were accompanied by increased psychotic symptoms and reduced impulse control. The results of the study thus indicated that the co-occurrence of psychotic symptoms, impaired impulse control, and aggressive behavior in schizophrenia should be linked to a neurobiological basis [2].

A study of two groups of patients with schizophrenia: perpetrators of murder and patients not exhibiting aggressive behavior revealed that the representatives of the first group were characterized by significantly higher impulsiveness (measured by the BIS-11 Scale) and aggressiveness (measured by the Buss-Warren BWAQ Aggression Questionnaire) [30]. However, so far, brain imaging methods do not allow us to clearly identify the areas that are associated with high levels of impulsiveness as measured by psychological tests. Impulsiveness demonstrated by the Eysenck Questionnaire was associated with activation of the right inferior frontal gyrus, right inferior parietal lobule and insular cortex, confirmed by the Barratt Scale with the activity of the left superior temporal gyrus and middle frontal gyrus [22], which suggests rather different locations of the centers responsible for individual components of impulsiveness.

Changes in neurotransmitters

In the etiology of aggressive behavior, apart from the serotonin hypothesis, attention is paid to the importance of the dopaminergic and vasopressor systems. A role in this respect is also attributed to norepinephrine, gamma-aminobutyric acid, and the neuropeptide cholecystokinin (CCK) [31, 32].

Serotonin signaling is the main modulator of emotional behavior, not only anxiety, but also impulsiveness and the associated aggression. It integrates complex brain functions such as cognitive and motor activity and sensory data processing, which has special significance for the image and severity of impulsiveness. It has been established that the level of 5-HIAA (5-hydroxyindoleacetic acid), a metabolite of serotonin, in the brain and cerebrospinal fluid is reduced in people who are impulsively aggressive and prone to acts of auto aggression [33].

Simultaneously, in the process of regulating the level of impulsiveness, complex interactions occur between the serotonergic and dopaminergic systems [15]. The dopaminergic nucleus accumbens plays a role in regulating impulse control – its task is to control goal-directed behavior [34]. The increase in dopaminergic activity is associated with strengthening the response to punishment and reward and therefore with limiting behaviors resulting from cognitive impulsiveness [35, 36].

The noradrenergic system, in turn, influences the level of impulsiveness conditioned by emotional state. In stressful situations, the noradrenergic activity of the locus coeruleus increases, which neutralizes the inhibitory functions of the frontal cortex.

On the one hand, it has a defensive meaning in dangerous situations, on the other – pathological intensification of this type of transmission results in increased impulsiveness [37]. The functioning of the glutamatergic system is also important for the control of emotional reactions – blocking the NMDA receptor causes appearance of impulsive behaviors [38].

Genetic basis of impulsiveness

Among mental disorders, the highest level of impulsivity is associated with the diagnosis of schizophrenia, schizotypal disorders, and bipolar affective disorders [39]. On the other hand, a study comparing the level of impulsiveness among healthy people, people suffering from schizophrenia, schizoaffective disorder, and bipolar disorder showed that people with schizoaffective disorder and bipolar disorder show a significantly higher level of impulsiveness than patients with schizophrenia, and the latter are characterized by a much higher intensity of impulsiveness than healthy people [40]. The most likely genes responsible for molecular mechanisms linking schizophrenia and depressive disorders are: *GRIN1*, *GPM6A*, *SEPTIN4*, *TPH1*, *TPH2*, *CACNA1C*, *CACNB2*, and *BCL9*. Cellular and molecular models underlying these disorders show that most of them can be classified as synaptopathies or defects in synaptic function and plasticity [41]. A genome-wide association study of five major psychiatric disorders found that single nucleotide variant (SNV) at chromosomal loci 3p21 and 10q24, as well as *CACNA1C* and *CACNB2* in genes encoding calcium channel subunits, are

largely associated with schizophrenia, bipolar disorder, attention deficit hyperactivity disorder with attention deficit (ADHD), and autism (ASD) [42], i.e., conditions in which we are dealing with increased impulsiveness and accompanying aggressive behavior.

On the basis of genetic-related neuroimaging studies, it is known that genetic variations mediate impulsiveness modulation by affecting specific brain areas, neurotransmitter systems, and the peripheral nervous system [26]. The relationship between polymorphisms in the genes of dopaminergic, serotonergic, and noradrenergic pathways in the central nervous system, including the dopamine transporter, D2 receptors, D4 and D5 receptors, serotonin transporter SLC6A4 [43], serotonin receptors [44], tryptophan hydroxylase [45], catechol-O-methyltransferase (COMT) [46], and various forms of aggressive behavior has been confirmed.

In terms of individual differences in impulsive and aggressive behavior, genetic variability in monoamine oxidase A (MAOA) and its impact on serotonergic conduction within corticolimbic circuits play a particular role [47]. A functional single nucleotide polymorphism in the *COMT* gene, Ala72Ser, is associated with aggressive behavior in schizophrenia [48].

In a study of people of European descent using the Barratt Impulsiveness Scale-11, its participants were genotyped for three single nucleotide polymorphisms associated with catecholaminergic neurotransmission: DRD2/ANKK Taq1A, C957T DRD2 and Val158Met of the *COMT* gene. A significant impact of Val158Met and C957T on the increase in BIS-11 scores was confirmed, but no significant associations were found between the scores on this scale and Taq1A [49]. It was found that in the case of the Val66Met brain-derived neurotrophic factor (BDNF) gene, carriers developed increased stress-induced psychotic symptoms with reduced cognitive abilities. The serotonin transporter gene SLC6A4, on the other hand, has been linked to the risk of increased stress reactivity, which may be associated with triggering impulsive action. It has been found that stressful events occurring early in life in schizophrenic patients can cause long-term neurobiological changes and alterations in genes related to the hypothalamic-pituitary-adrenal (HPA) axis. Genes identified in psychotic disorders interact with genes of the hypothalamic-pituitary-adrenal (HPA) axis leading to long-term dysregulation of the stress hormone system. The result is a reduction in the ability to control behavior [50].

In recent years, the role of neuroligins and neurexins in explaining the biological basis of impulsiveness has become increasingly important. In humans, neuroligins comprise a group of S genes that, like neurexins, are further differentiated by alternative splicing. Depending on the type of protein, they act on excitatory or inhibitory synapses. Genetic variants in the *NLGN2* gene have been found in patients with schizophrenia, autism, and anxiety disorders, however, they have so far not been confirmed to have a direct link in humans to levels of impulsivity or aggression. This issue requires further genetic analysis, which is encouraged by the results of studies in animal models. Animal studies show that *NLGN2* in the hippocampus are strongly involved in maintaining the balance between the process of excitation and inhibition in the brain, thus influencing the modulation of social and emotional behaviors [51]. Other studies on animal models allow us to conclude that single mutations of the neu-

roligin 2 (*NLGN2*) gene encode a cell adhesion particle important for the formation of GABAergic synapses. They reduce GABAergic transmission in the hippocampus and cause increased anxiety behavior, impaired inhibition of impulsive actions, cognitive deficits, and impaired reactions to stress in mice [52].

Abnormal synaptic plasticity in various brain areas, including amygdala, leads to impulse control deficits that are found in ADHD, schizophrenia, depression, and addiction. In the case of animals, an impulsiveness locus (*Impu1*) was identified containing the neuregulin 3 (*NRG3*) gene, the expression level of which determines the level of inhibitory control. MicroRNAs (miRNAs) are potent regulators of gene expression, but their role in impulsiveness as well as in the control of *NRG3* expression or amygdala malfunction is not yet well understood [53].

Neurexins are a family of synaptic adhesion proteins involved in formation and maintenance of synaptic structures, as well as synaptic functions. They are present in the presynaptic membrane of both inhibitors and excitatory synapses. Neurexins bind to other proteins: neuroligins, dystroglycans, neuronal transmembrane proteins, cerebellum, calstentensins, latrophilins, and neuroexophilins. Larger deletions, duplications, but also missense mutations were found in patients with autism spectrum disorders and schizophrenia [54]. It is suspected that transcriptomic and splicing deregulation of genes encoding neurexins is important in the occurrence of neurodevelopmental diseases not only in patients with rare variants of these genes, but also in people who are not carriers of genetic variants who are exposed to environmental factors that initiate the disease process, e.g., drugs [55].

Discussion

Prediction of aggressive behavior in the case of people with schizophrenia spectrum disorders, who constitute a dominant group of insane offenders of prohibited acts, is one of the tasks of forensic psychiatry [1]. Imperfections in the assessment of this risk may affect not only the perpetrators themselves, but also cause negative social consequences (repeated violations of the law, new psychiatric hospitalizations, rising costs of forensic psychiatry). In the light of the results of research on biological basis of aggression in this group of violators, estimating the probability of aggression solely on the basis of an analysis of the perpetrator's psychopathological image, his personality traits, cognitive deficits or social functioning disorders becomes insufficient [2].

One of the factors that could improve assessment of a threat posed by people with schizophrenic disorders is an analysis of their impulsiveness, especially in connection with affective symptoms [40]. It remains an open question which of the psychological models of impulsiveness may be the most useful in assessing the likelihood of aggression in this group of perpetrators, although the one developed by Barratt [9, 13] is considered one of the most useful. This scale could be routinely used to assess impulsivity during forensic psychiatric and psychological examinations in criminal cases [9].

During forensic psychiatric assessment of perpetrators of prohibited acts with schizophrenic symptoms, they are generally subjected to brain imaging tests, but this is done almost exclusively for clinical diagnostic purposes (they are used to confirm

or exclude the organic basis of psychotic disorders). Still, the results of these studies cannot be used to assess the biological determinants of impulsivity. Some brain imaging studies suggest links between specific centers in the central nervous system and impulsivity among people with schizophrenic disorders [24, 27, 29], but their results are so inconclusive that they cannot currently be used either in clinical practice or even more so in forensic psychiatric practice. Further development of research in this area is to be expected, which may, in the future, enable its use when estimating the risk of violent behavior in this group of offenders.

An important extension of knowledge about biological basis of impulsiveness is data on abnormalities in functioning of individual neurotransmitter systems. First of all, there is a dysfunction in the serotonergic, dopaminergic and noradrenergic systems and abnormal relationships between them [33]. A more precise definition of these disorders in the context of impulsiveness will probably facilitate determination of adequate pharmacotherapy aimed not only at symptomatic but also behavioral improvement.

Increasing attention is being paid to the importance of genetic determinants of impulsiveness, also among patients with schizophrenia spectrum. The results of research on explaining the molecular mechanisms linking schizophrenia and other mental disorders are optimistic. Genetic studies confirm that individual genetic variants mediate the modulation of impulsiveness in different areas and at different levels of the nervous system [26]. They are further deepened by genetic research on relationships between individual neurotransmitter pathways and various forms of impulsiveness and aggressive behavior [56].

Neuroligins and neurexins are of particular importance in explaining the etiology of impulsiveness, and although research is conducted primarily on animal models, their results are so promising that it can be expected that they may soon provide a lot of important information on the etiology of impulsiveness in humans [55].

However, understanding the complex molecular basis of impulsive behavior requires developing a systemic network to recognize the interplay of genes and their products. Research on the genetic basis of impulsiveness disorganizing behavior in the context of synaptic abnormalities will be a step towards diagnosing particularly dangerous patients with schizophrenia spectrum. They will probably also allow us to determine the level of biological determination of individual forms of impulsiveness (motor, cognitive, and the one resulting from lack of planning), which constitute the basis for aggressive behavior. Individuals confirmed to primarily exhibit genetic etiology of impulsivity are likely to be characterized by a consistently elevated level of it and decreased stress resilience [50]. In their case, an increased risk of aggressive behavior should be expected. In patients without confirmed genetic underpinnings, one should expect not so much impulsivity as a constant trait, but rather a tendency to impulsive reactions accompanying other mental health issues. Distinguishing between these two groups, beyond enabling a more precise assessment of aggression risk, will likely contribute to a more accurate selection of therapeutic methods, reducing their compulsory hospitalization and, consequently, lowering the costs of treating offenders of criminal acts [6]. Genetic research in neuropsychiatric diseases has made signifi-

cant progress, providing new information on the genetic etiology of mental disorders, thus paving the way to the creation of “precision psychiatry,” in which the patient’s individual genetic profiles will play a key role [57].

Numerous studies refer to the individual nature of disorders, but the latest ones indicate that, apart from hereditary issues, these are heterogeneous disorders, where we observe thousands of interacting genetic variants. Genome-wide studies (GWAS) conducted on large groups of patients have led to the identification of specific gene loci associated with an occurrence of serious mental disorders, including schizophrenia, autism, and severe mood disorders. Interpretation of such large-scale results has allowed us to draw one of the most convincing conclusions regarding changes in synaptic functions in autism spectrum disorders and schizophrenia [58]. For example, the role of previously described adhesion molecules, such as neuroligins (NLGN) in the postsynaptic element and their ligands, neuroligins (NLGN) in the postsynaptic element, are the main proteins organizing the formation and functioning of synapses. It has been found that mutations in the *NRXN*, *NLGN* and *SHANK* group genes are high-risk factors for the development of neuropsychiatric disorders [59].

As for the future of the development and direction of genetics in psychiatry, it should be seen in the nature of the genotype-phenotype relationship, in relation to the biology of specific mental disorders, which has not yet been fully discovered [60]. Whole genome sequencing (WGS), performed on precisely defined groups of patients, may bring us closer to this. The advantages of WGS include its comprehensiveness, including the analysis of coding and non-coding sequences, better coverage of sequences and, in fact, entire genes that could not be easily sequenced before, as well as detection of genetic variability within the study group. This also ensures increased diagnostic efficiency. Moreover, it will enable creation of a catalogue of non-coding variability, which is assumed to significantly contribute to the development of mental disorders [57].

Following this approach, progress can be expected in the assessment of gene-gene interactions, gene networks in the assessment of systemic approaches, and the impact of environmental factors on the patient’s genome. Analysis of the epigenome as an interface/bridge between the genome and the environment is therefore expected to provide key insights into development of mental disorders. Genome-wide assessment of epigenetic marks such as DNA methylation or chromatin modifications has become possible thanks to advances in DNA sequencing methods and is constantly being developed [61].

One of the issues limiting the development of insightful neurodevelopmental analysis has been the inaccessibility to human brain tissue, which can now be overcome with stem cell approaches, which enable the study of neurons (derived from pluripotent stem cells) from patients in *in vitro* cell cultures. Also, research on cerebral organoids (3D cultures) as model systems may open new possibilities for precise monitoring of processes occurring at the cellular level. This may create the basis for revolutionizing pharmacological treatment, because to some extent it can reproduce the state of patients’ neuronal cells [62, 63]. Technological progress gives us enormous opportunities to thoroughly study neuropsychiatric disorders. Knowledge of these issues and innovative

research concepts will significantly influence development of psychiatric genetics and improve understanding of the biology of neurological disorders.

In summary, over the past decade or so, there has been a noticeable increase in interest in impulsivity, treated as a background to aggressive behavior exhibited by people with mental disorders, including those on the schizophrenia spectrum. They not only analyze the psychological determinants of impulsivity, but also take into account its biological background. Some of these studies focus on selected single aspects of impulsivity, while others look at combinations between different etiological factors: psychological, biological, situational, and environmental. Although at present most of the genetic research is theoretical in nature (many of which are based on animal models), the results are so promising that further dynamic developments should be anticipated for future use in clinical practice.

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