Response to Reviewers, Science editor, and Company editor-in-chief:

Thank you for your review of our paper and very valuable notes. Our responses are given in a point-by-point manner below. Our responses to the comments are below in blue (*the Reviewer's and Associate Editor's notes are in italics*). Changes to the manuscript are shown in red.

Reviewer #1

1. *Title: It does not mention that it is a review. Suggestion: It should be added to the title that it is a literature review and the type of review.*
   Answer: The title of the manuscript has been changed.
2. *The abstract summarizes and reflects the work described in the manuscript.*

3. *Key Words The key words reflect the focus of the manuscript.*

4. *Background: The manuscript adequately describes the background, current status, and significance of the study but does not describe but does describe the objectives of the review or the type of literature review it intends to conduct.*
   Answer: In line with your recommendation, the objectives of the review have been added.
   Lines # 166-169

5. *Methods: The manuscript does not describe the type of review it performed or the type of protocol it followed for that purpose. It does not present search criteria or article selection criteria. Without the review objectives and the research protocol, it is difficult to evaluate the review presented.*
   Answer: In line with your recommendation, the article selection criteria have been added.
   Lines # 170-178

6. *Results: The objectives and research protocol of this review were not specified, so the scope of this literature review is unclear*
   Answer: The objectives and research protocol have been added.
   Lines # 162-178

7. *Discussion: There is no specific chapter for discussion. Although does the manuscript adequately and appropriately interpret the results, highlighting the key points in a concise, clear, and logical manner of the findings in the review? Scientific significance and/or relevance of the topic to clinical practice is presented.*
   Answer: The discussion of the results was presented both directly in the text, following the original research data, and in the last section, which was renamed to "Discussion". The "Conclusion" section has been added separately.

8. *References: The manuscript properly cites the most recent references. The vast majority are less than five years old, although a small number are more than ten years old.*
   Answer: References with a publication date of more than 10 years represent either conceptual manuscripts or studies of very narrow subject matter that require replication using contemporary approaches.

9. *Quality of manuscript organization and presentation: The manuscript is well, organized and presented in a concise and coherent manner, although it does not meet the Guidelines for manuscript preparation, submission and format: Revision as stated in the journal.*

10. *Research methods and reporting: The Authors do not prepare their manuscript according to the standards for the type of manuscript and the appropriate category, according to the appropriate research methods and reporting.*

11. *Ethics statements: This manuscript is a review Suggestions to the authors: In the introduction they should clarify what kind of review they intend to carry out, what their objectives are, and present the research protocol (to understand if it meets the criteria and how and where the research was done) They should follow the journal's guidelines for submission of a review manuscript.*
    Answer to the points #9-11: In line with your recommendation, the objective and article selection criteria have been added.
    Lines # 162-178

Reviewer #2

1. *The topic is not clear. The title is "Neurobiological Risk Factors for Problematic Social Media Use: Vital Hypotheses and Upcoming Perspectives, but a large number of findings reviewed in this paper are related to Internet addiction, not problematic social media use (PSMU). Please pay attention to the emphasis of the article. The title should be changed to make it more relevant, or the content not related to PSMU should be cut.*
   Answer: In line with your recommendation, the title of the manuscript has been changed.
2. *Abstract and keywords are not strong enough to summarize the article.*
   Answer: In line with your recommendation, the abstract and keywords have been changed. Changes to the manuscript are shown in red.
   Lines # 127-136; 138-140

3. *There are some spelling and grammar errors, such as "ethnogeographic" and "a adolescent".*
   Answer: Additional language polishing was performed.

4. The Social Media Disorder Scale (SDMS) and Bergen Social Media Addiction Scale were mentioned in the manuscript, but their specific reliability and validity values were not reported.
   Answer: Reliability and validity values were added.
   Lines # 276-277

Science Editor's comments to the authors:

The manuscript has been peer-reviewed, and it' s ready for the first decision. Language Quality: Grade B (Minor language polishing) Scientific Quality: Grade D (Fair).

Answer: Additional language polishing was performed.

Company editor-in-chief's comments to the authors:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Psychiatry, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, the author(s) must add a table/figure to the manuscript. There are no restrictions on the figures (color, B/W) and tables. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Answer: The Figure №1 was added to the manuscript.

NEUROBIOLOGICAL RISK FACTORS FOR PROBLEMATIC SOCIAL MEDIA USE AS A SPECIFIC FORM OF INTERNET ADDICTION: A NARRATIVE REVIEW

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Abstract.

Problematic social media use (PSMU) is a behavioral addiction, a specific form of problematic Internet use associated with the uncontrolled use of social networks. It is typical mostly for modern adolescents and young adults, which are the first generations fully grown up in the era of total digitalization of society. The modern biopsychosocial model of the formation of behavioral addictions, postulating the impact of a large number of biological, psychological, and social factors on addictive behavior formation, may be quite applicable to PSMU. In this narrative review, we discussed neurobiological risk factors for Internet addiction with a focus on current evidence on the association between PSMU and structural / functional characteristics of the brain and autonomic nervous system, neurochemical correlations, and genetic features. A review of the literature shows that the vast majority of the mentioned neurobiological studies were focused on computer games addiction and generalized Internet addiction (without taking into account the consumed content). Even though a certain number of neuroimaging studies have been conducted for PSMU, there is practically no research on neuropeptide and genetic associations for PSMU to date. This fact points to the extremely high relevance of such studies.

Key words: Internet addiction; Problematic social media use; Neurobiology; Addictive behavior physiopathology; Brain physiopathology; Neural pathways physiopathology; Genetics; Gene Frequency

Core Tip: The analysis of sources showed that the vast majority of neurobiological research was focused on the study of computer games addiction and generalized Internet addiction (without taking into account the content consumed). There is practically no research on neuropeptide and genetic associations for problematic social media use to date. This fact points to the extremely high relevance of such studies.

The last two decades have been characterized by an avalanche-like increase in Internet use among all social groups, especially among adolescents and young adults [1, 2]. The advantages associated with the widespread introduction of Internet technologies into people's daily lives are undeniable (for example, quick access to a large amount of

information and various services, rapid dissemination of news on a global scale, the introduction of Internet technologies related to health, etc.). However, a certain number of Internet users, mainly adolescents, and young adults, experience the phenomenon of Internet addiction or "problematic/compulsive use of the Internet", characterized by loss of control over being online, obsessive craving for various types of Internet activity, which often causes the formation of a wide range of psychosocial and psychosomatic problems [2, 3]. The global concern about the impact of problematic Internet use (PIU) from the public and social health points of view became especially acute during the COVID pandemic when each person had to use the Internet more often, and initially, predisposed individuals were losing control, showed more and more signs of pathological addictive behavior when diving into the network [4]. In particular, this trend has affected the most technologically advanced segments of society – the first generations who grew up surrounded by the Internet and gadgets – adolescents and young adults [5]. The situation can be significantly aggravated by the neurophysiological consequences of the pandemic, predisposing to the development of depression and anxiety, which are important risk factors of problematic social media use (PSMU) [6].

The modern "component bio-psychosocial model" of behavioral addiction formation postulates an individual combination of genetic / biological, psychological, social, and cultural factors leading, in the case of PSMU, to overuse of social media and negative consequences (Figure 1).

In this narrative review, we shall discuss neurobiological risk factors for Internet addiction with a focus on current evidence on the association between PSMU and structural / functional characteristics of the brain and autonomic nervous system, neurochemical correlations, and genetic features.

To find relevant publications, a search was conducted in PubMed, Scopus, and Web of Science for English-language sources using the following keywords and MeSH terms: "Internet addiction", "Problematic social media use", "Pathological social network use", "Social media", "Social Networking", "Specific Internet addiction", "Video game addiction", "Gaming disorder", "Neurobiology", "Behavior, Addictive / physiopathology", "Brain / physiopathology", "Sympathetic Nervous System", "Parasympathetic Nervous System", "Neural Pathways / physiopathology",

"Neurotransmitters", "Biochemical correlates", "Twin study", "Genetics", "Gene Frequency", "Genetic Predisposition to Disease", "Polymorphism, Single Nucleotide".

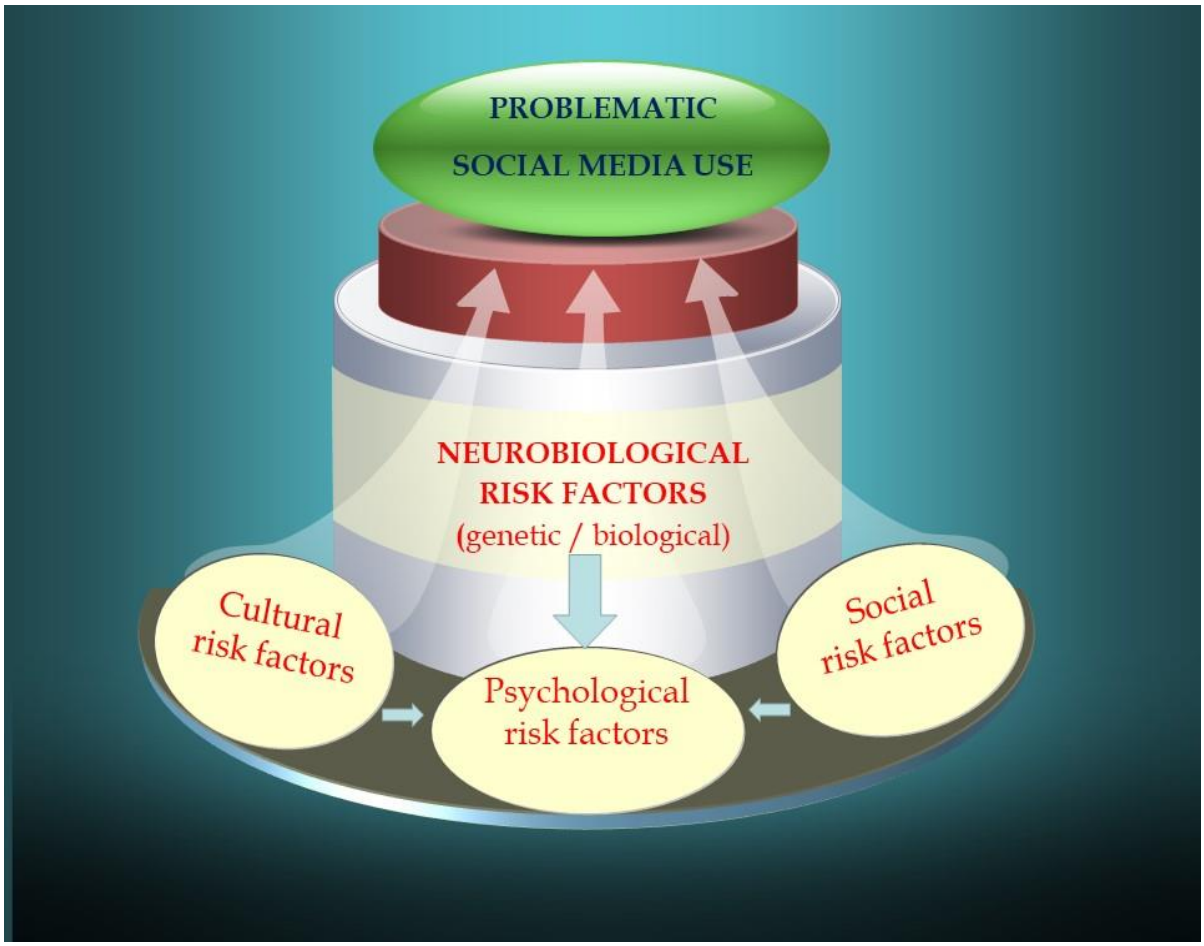

Figure 1. Component bio-psychosocial model of problematic social media use.

Terminology.

The phenomenon of Internet addiction [7, 8] was first described in the mid-1990s. It has caused numerous scientific, clinical, and social debates since its inception to the present. From the classical psychology and psychiatry point of view, addictive online behavior is a relatively new phenomenon of behavioral (non-chemical) addiction, which currently has no accepted formal definition. Specialized literature offers such interchangeable terms as the recently proposed "problematic interactive media use" [9], as well as more traditional "problematic Internet use", "pathological Internet use", "compulsive Internet use", and, finally, "Internet addiction". Experts of the European Network for Problematic Usage of the Internet (European research group) recommended

in a recent review (2022) to use the term "problematic Internet use", as the most appropriate at this moment [4].

All of the above are umbrella terms, i.e., reflect generalized (without reference to specific content and technology) PIU. Five main specific types of online activity can be considered potentially addictive by now: problematic video game use, PSMU, problematic Internet pornography use, Internet gambling, and web surfing addiction [10, 11].

Only one of these five addictive behavior types, namely the problematic use of video games, is currently officially considered a mental disorder (*Internet Gaming Disorder*, DSM-5; American Psychiatric Association, 2013; *Gaming Disorder*, ICD-11, 2019). Recently, other specific forms of PIU have also been singled out: online gambling disorder (it also includes intensive betting on online exchanges), online buying-shopping disorder, Internet streaming disorder, cyberchondria, cyberbullying, and digital hoarding [4].

PSMU is a behavioral addiction, a specific form of PIU associated with the uncontrolled use of social networks. It is typical mostly for modern adolescents and young adults, which are the first generations fully grown up in the era of total digitalization of society. There are currently no universally recognized and official criteria for the diagnosis of PSMU. The European Network for Problematic Usage of the Internet (European research group) suggests the following definition [4]:

PSMU is a persistent state of control loss when using social networks, manifested by:

- violation of control over interaction with social websites (for example, in terms of time, frequency, and duration of use);
- predominance of time spent on social networks over other life interests and activities;
- negative consequences, i.e., the use of social networks leads to significant distress or deterioration in personal, family, social, educational, professional activities, or other important areas of functioning;
- continued or increased use of social networks, despite the negative consequences (for example, poor school performance, negative impact on health, social isolation, interpersonal conflicts, neglect of duties);
- duration, i.e., the use of social networks can be continuous or episodic and repetitive but manifests itself over a long period (at least 12 months).

Although the criteria for the diagnosis of PSMU are not formally established, the existing validation methods using questionnaires are based on the interpolation of classical symptoms for chemical and non-chemical types of addictive behavior [12]. Currently, there is a consensus on diagnostic criteria that clearly distinguish the pathological component of addiction from the normal daily use of the Internet by adolescents: the clinical diagnosis of PSMU, as well as generalized Internet addiction, should include six obvious signs [11, 13, 14]:

- Salience and mood modification, such as behavioral, cognitive, and emotional preoccupation: the growing importance of a social network for an adolescent in his or her system of interests and values; the use of a social network leads to a positive change in the emotional state;
- Compulsivity and loss of control: an obsessive desire to use the social network, impulsivity, loss of time control, excessive use of the social network (especially while reducing the allocated time for other activities);
- Tolerance: the need to spend more and more time communicating on a social network, including to alleviate episodes of dysphoria;
- Withdrawal /abstinence symptoms: mood changes in the absence of access to a social network (depression, anxiety, aggressiveness);
- Conflict, impaired role performance: loss of previous interests and entertainment, loss of educational, cultural, sports, and other opportunities as a result of excessive use of social networks; disputes and lies regarding the use of the social network; continued use of social networks, despite the negative consequences.
- Relapse: rapid return to the use of the network after abstinence, unsuccessful independent attempts to control the use of the social network.

However, PSMU must be distinguished from intensive adaptive use of social networks. Adaptive intensive use of social networks itself does not have obvious negative consequences, has little effect on the parameters of well-being, and in many individual cases can play a positive role in the development of an adolescent by increasing a "social capital" [15, 16]. Thus, Boniel-Nissim and Alt discovered, by investigating the use of social networks during the COVID epidemic, that intensive adaptive use of the social network

is characteristic of students with positive mental health qualities and greater family support, whereas PSMU is associated with a sense of loneliness, low life satisfaction, which is closely related to low self-esteem, and less support from friends [17].

Prevalence.

The latest summarized data show that the average prevalence of PSMU among adolescents in 29 European countries is 7.4% [18]. The recent systematic review by Cheng *et al*. [19] showed a high ethnic and geographic heterogeneity of PSMU prevalence within 5–26%: the main modifying factors were the method of dependency classification (monothetic/polythetic models and cut-offs), as well as geographical and cultural factors. The highest levels of PSMU prevalence are registered in collectivist societies in Asia and Africa [19]. Recent cross-national analysis of the psychometric characteristics from the Social Media Disorder Scale (SDMS) questionnaire among adolescents from 44 countries has shown high levels of its validity and reliability (comparative fit index and Tucker–Lewis index = 0.963 and 0.951, root mean square error of approximation = 0.057) [20]. SDMS is recommended by the research group European Network for Problematic Usage of the Internet as preferred, since it evaluates primarily the psychopathological aspects of addiction, while the recently criticized Bergen Social Media Addiction Scale questionnaire does not clearly distinguish between simple excessive or prolonged use of social networks from pathological one, with signs of addiction [4]. Prevalence data obtained by the authors of the SMDS questionnaire for the Dutch teenage community are 7.3–11.6% [21]. Similar results were obtained in other studies using SMDS: a Dutch sample in a longitudinal study – 9.9–10.0% [22], a representative sample of 3,408 Finnish adolescents – 9.4% [23], a large sample of Russian adolescents (n = 4514) – 8.0% [24].

Psychiatric and somatic comorbidity.

A large number of foreign studies have convincingly shown the pronounced comorbidity of Internet addiction with a wide range of psychopathological conditions [25, 26]. Thus, the meta-analysis of Roger *et al*. demonstrated the comorbidity of Internet addiction with depression (Odds ratio (OR) = 2.77, confidence interval (CI) = 2.04–3.75), anxiety disorders (OR=2.70, CI = 1.46–4.97), attention deficit hyperactivity disorder (OR = 2.85, CI = 2.15–3.77). Carli *et al*. have revealed in their systematic review that depressive disorder and attention deficit hyperactivity disorder have the greatest connection with

Internet addiction, while anxiety disorder, obsessive-compulsive disorder, social phobia, and aggressive behavior also show a smaller but significant connection. Similar conclusions were drawn in a recent systematic review [25]. The study by Durkee *et al*. [27], which included a representative sample of 11,356 adolescents from 11 European countries, convincingly showed the association of Internet addiction with self-harming and suicidal behavior, as well as with depression and anxiety. The same data were obtained in the study by Jiang *et al*. [28]. A recent meta-analysis by Shannon *et al*. has shown that PSMU, as a specific form of Internet addiction, also reveals a moderate, but statistically significant, association with depression, anxiety, and stress [12]. Another recent meta-analysis demonstrated a significant but weak negative association of PSMU with life satisfaction and self-esteem (as parameters of well-being) and a moderate positive association with depression and loneliness (as indicators of distress) [29].

At present, not much is known about the association of Internet addiction with psychosomatic diseases, although such a connection is highly likely, given the presence of common pathogenesis factors (anxiety-depressive and obsessive-compulsive disorders). The study by Wei *et al*. [30] based on an Internet survey demonstrated the association of Internet addiction with chronic pain syndromes, which the authors link with psychosomatic diseases and muscle overstrain. The study conducted by Cerutti *et al*. did not reveal a statistically significant association between Internet addiction and tension headache/migraine, although, in general, somatic symptoms were more often reported in the Internet addiction group [31]. In addition, it was discovered that PIU among adolescents was associated with chronic conditions (OR = 1.58, CI = 1.11–2.23), back pain (OR = 1.46, CI = 1.04–2.05), overweight (OR = 1.74, CI = 1.03–2.93), musculoskeletal pain (OR = 1.36, CI = 1.00–1.84), and also with sleep disorders (OR = 2.16, CI =1.62–2.88) [32, 33]. According to a recent systematic review, a wide range of somatic health problems are associated with smartphone addiction among adults [34]. A general decrease in immune functions was observed in Internet-addictive individuals, which the authors link with a common risk factor, i.e., stress, which can affect the activity of the sympathoadrenal axis and increase cortisol production [35]. It is characteristic that the high activity in the sympathetic part of the autonomic nervous system was detected when analyzing the heart rate of adolescents with Internet addiction [36, 37]. A decrease in the quality of life, including the parameters of somatic health, was demonstrated in a

systematic review by Masaeli and Billieux [38]. A pronounced connection between Internet addiction with the general level of somatization was revealed among young adults [39].

Pathogenesis of Internet addiction from neurobiology point of view.

To date, several etiopathogenetic models of the formation of Internet-dependent behavior among adolescents and young adults have been proposed [40]. Some researchers suggest the presence of mainly neurobiological risk factors linked with the lack of maturity in certain parts of the adolescent brain, which is manifested by insufficient effectiveness of volitional control, high impulsivity, and an overly activated brain reward circuitry [41, 42]. However, the most recognized by researchers at present is the "component biopsychosocial model", which assumes a combination of psychosocial problems and neurobiological risk factors [40, 43-45].

Middle and late stages of adolescence in brain development are characterized by different time frames of the formation of the limbic system and prefrontal cortex lobes [46]. The prolonged development of the prefrontal cortex in comparison with the limbic system during adolescence leads to weakened inhibition from cortex lobes concerning underlying subcortical structures and increased impulsivity, which contributes to a high risk of addictive behavior [47].

To date, a large number of studies have been devoted to the pathogenesis of Internet addiction using various neuroimaging techniques, including magnetic resonance imaging (voxel-based morphometry, diffusion tensor imaging; functional magnetic resonance imaging) and nuclear magnetic resonance of the brain (positron emission tomography; single photon emission computed tomography). These techniques revealed a number of the following structural changes in the brain associated with Internet addiction [48-50]: gray matter density reduction in various areas, including the prefrontal and orbitofrontal cortex, as well as supplementary motor area [51], abnormal functional activity of brain regions linked to reward addiction [41], activation of sensory-motor synchronization with simultaneous reduction of audiovisual synchronization [52], activation of brain regions associated with the formation of irresistible desires and impulsivity, an increase in glucose metabolism in brain regions associated with impulsivity, dependence on rewards and the desire to repeat experienced sensations [53], an increase in dopamine secretion followed by decreased availability of dopamine

receptors in the striatum [54]. Meta-analysis of 40 neurophysiological studies of PIU has shown that, regardless of the content, Internet-dependent behavior is characterized by a significant violation of inhibitory control, stop-signal task, decision-making, and working memory [55]. The meta-analysis by Zhang *et al*. has revealed the presence of a common pattern in a brain structural change related to chemical and behavioral addictions: changes in prefrontal and insula areas associated with increased impulsivity [56]. Several meta-analyses and reviews have been published recently: structural and functional brain alterations for a specific form of PIU – computer games addiction [57-59]. The features of electroencephalography in Internet addiction were analyzed in a recent review by Sharifat and Suppiah [60]. Distinctive characteristics of functional electroencephalography were revealed among patients with computer game addiction [61].

It should be noted that most of the above-mentioned studies have been conducted for cases of computer games addiction or generalized (undifferentiated by the content consumed) Internet addiction. The recently proposed for various types of behavioral addictions updated Interaction of Person-Affect-Cognition-Execution (I-PACE) model theoretically substantiates the neurobiological mechanism of addictive behavior, which consists in an imbalance between structures of frontostriatal circuits (limbic/reward-oriented brain circuits and prefrontal control) [62]. The model has been intensively studied for gambling and gaming disorders, but not for PSMU. Despite this, a line of structural and functional neuroimaging findings concerning the I-PACE model for PSMU was published to date [63-68]. Neuroimaging studies for PSMU were analyzed by Wegmann *et al*. [69]; a conclusion was made about the significant association of PSMU with reward processing and reinforcement learning. A recent study by Sadeghi *et al*. has revealed that email addiction positively correlates with depression and gray matter volume of the left rostrolateral prefrontal cortex closely involved in cognitive processes [70].

There is some evidence of autonomic nervous system dysfunction involvement in the pathogenesis of Internet addiction, in particular, by the imbalance of the sympathetic and parasympathetic divisions [71, 72]. A general decrease in immune functions was revealed among Internet-addictive individuals. The authors link this fact with a common risk factor, i.e. stress, which can affect the activity of the sympathoadrenal axis and increase cortisol production [35]. The role of chronic stress in the formation of PSMU has been shown by several studies [12, 73, 74]. It is characteristic that the high activity of the

autonomic nervous system's sympathetic part was observed when analyzing the heart rate of adolescents with Internet addiction [36, 37]. Data on the level of cortisol for Internet addiction are contradictory [75-77]; additional research is required, in particular, concerning the long-term cortisol content, which can be a good marker of chronic stress and mental problems [78].

Several neurotransmitters and neurotrophic factors may be involved in the neurobiological mechanisms of Internet addiction formation [79-81]. Neurochemical pathways include metabolic disorders of dopamine, serotonin, opioids, and some other neurotransmitters that affect reward processing, executive functioning, salience attribution, and habit formation, as well as in the case of substance-use disorders [82]. The participation of these neurotransmitters is partially confirmed by the effectiveness of some pharmacological agents controlling the corresponding neurochemical pathways [83, 84]. Exercise-based interventions also may be efficient for Internet addiction (including PSMU) [85], by regulating the autonomic nervous system, the morphology of some parts in the central nervous system, and the exchange of neurotrophic factors and neurotransmitters, in particular dopamine [72].

Oxytocin, which is called the hormone of trust, social connection, and emotional attachment, is promising for the PSMU study. It plays an extremely important role in establishing emotional social contacts, including those using social networks [80, 86]. Bonassi *et al*. showed that a low level of parental care was associated with low activity on Instagram for carriers of the A-allele in the polymorphic region rs2254298 for the oxytocin receptor gene [87]. The same group of researchers identified a greater number of followers among carriers of the A/A genotype in the region rs53576 for the oxytocin receptor gene in comparison with carriers of the G-allele [88].

A significant number of studies show a pathophysiological relationship between the functioning of the oxytocinergic system and the formation of various forms of addictive behavior [89]. The effectiveness of exogenous oxytocin in the treatment of various addiction types has been shown both in experimental animal studies [90] and in a whole series of clinical studies [89]. It is assumed that the relief of physical symptoms and an increase in emotional tone during withdrawal, reduction of anxiety, increased susceptibility to verbal interventions, facilitating the restoration of social contacts, and, finally, the physiological reduction of established tolerance are the main mechanisms of

oxytocin therapeutic impact for chemical addictions. The hypothesis of oxytocin antistress effect as a possible protective factor looks convincing since psychological stress is an important etiological cause of the formation of pathological addictions [91]. The antistress effect of oxytocin is realized by inhibition of excessive stress activation of the hypothalamic-pituitary-adrenal axis, regulation of the mesolimbic dopamine reward system, and production of corticotropin-releasing hormone.

The following are promising neurotransmitters and neurotrophic factors in addition to oxytocin, whose role in the pathogenesis of addictive Internet behavior in adolescents is also highly probable, but still insufficiently studied:

- Melanocortin (α-Melanocyte-stimulating hormone). According to the recent studies by Orellana *et al*., the important role of melanocortin in the formation of pathological addictions is assumed [92]. There was a tendency to increase melatonin levels in the presence of computer games addiction [93];
- Neurotensin. It is actively involved in the modulation of dopamine signaling and the formation of pathological addictions, attempts are being made to treat some types of addictions with synthetic neurotensin [94];
- Orexin. It is supposed to be involved in the formation of sleep disorders and addictive behavior [95]. Choi *et al*. demonstrated an increase of orexin in adolescents with Internet gaming disorder [93];
- Substance P (neurokinin A). Impairment in the production of substance P is considered to be associated with the formation of various pathological addictions; active attempts are currently being made to treat addictions by modulating the activity of neurokinin receptors [96, 97];
- Brain-derived neurotrophic factor (BDNF). This is a neurotrophic factor that plays a role in the formation of addictions [98, 99]. Data on the association of BDNF expression with Internet-addictive behavior are contradictory. Some authors found elevated plasma levels among addicts, the others did not confirm such an association [72, 81]. A recent study by Choi *et al*., which has been mentioned above, found no direct link between addiction and BDNF levels, although it revealed a negative correlation with the time spent playing a computer game [93].
- Glial cell line-derived neurotrophic factor (GDNF). It is a neurotrophic factor that plays an important role in supporting the function of dopaminergic neurons. A

decrease in the level of GDNF in plasma was detected among Internet gaming addicts; besides, the expression of BDNF was negatively correlated with the severity of computer games addiction [100].

It is important to note that the vast majority of studies on neuropeptides and neurotrophic factors have been conducted for computer game addiction, as in the case of neuroimaging and neurophysiological research methods.

Genetics of Internet addiction.

Unlike other types of addictive behavior (for example, substance abuse or gambling), a very small number of studies have been devoted to the search for genetic predictors of Internet addiction. For example, the first twin study was conducted in 2014: the authors managed to prove the presence of an innate component based on the results of a survey of 825 adolescents from the Chinese population. The component was estimated at 58–66% [101]. Similar results were obtained a little later in the study of England (20–49%, 2023 [102]) Dutch (48%, 2016 [103]), Australian (41%, 2016 [104]), and German (21–44%, 2017 [105]) twin cohorts. Positive genetic correlations (20–40%, 2012) were also discovered in the study of various mobile phone use patterns by twins [106]. Although these data are limited by the volume of samples and various ethnic and geographic conditions, there is likely a tendency for a greater contribution of genetic factors in males.

Thus, the presence of a genetic component in Internet addiction formation has been convincingly shown by twin studies by the example of different populations, but no specific genes involved in the mechanisms of such heritability have been identified. Small pilot studies, however, verified polymorphic regions of nine candidate genes, the following are among those:

- rs1800497 (dopamine D2 receptor (DRD2) gene, Taq1 A1 allele) and rs4680 (methionine variant of dopamine degradation enzyme catecholamine-o-methyltransferase (COMT) gene) – the first of such studies (2006–2007) conducted among adolescents in South Korea and showed a connection of minor alleles associated with low dopamine production (rs4680) and a low number of dopamine receptors in the prefrontal cortex (rs1800497) with the presence of pathological

adherence to Internet games [107]. At the same time, *DRD2* A2 allele (high-activity) homozygotes and A1 allele (low-activity) carriers demonstrated no significant differences concerning Internet addiction; neither differences were revealed when comparing COMT high-activity (H) variant homozygotes and low-activity (L) variant carriers [108].

Later, the association of the C allele carrier rs1800497 (*DRD2* gene) with computer games addiction was confirmed for young adults [109]. Another study did not prove such a fact [110]. It is known that the DRD2 gene is in linkage disequilibrium with the *ANKK1* gene, which plays a significant role in the formation of chemical addictions [111]. Therefore, by now, it is not possible to accurately establish the association of Internet addiction with the reception of dopamine at the DRD2 level [45].

The association of the homozygous variant Val/Val (GG) rs4680 (Val158Met, *COMT* gene) with addiction to computer games was further confirmed by the study by Yen *et al*. in 2022 [112];

In addition, a recent study by Kim *et al*. showed that the presence of interpersonal stress for *DRD2* rs6277 T allele and rs1800497 Taq1 A1 allele showed higher scale values of computer games addiction [113].

- rs6277 (promoter of the *DRD2* gene, *141C Ins/Del* polymorphism) – although a direct association between rs6277 polymorphism and Internet addiction has not been established, the *-141C* polymorphism may play a role in the pathogenesis of addiction as a mediator of temperament characteristics [110];
- The dopamine D4 receptor gene (DRD4 gene, VNTR polymorphism in exon 3) – as it was shown, the carriers of DRD4 4R/4R variants are more predisposed to the formation of generalized Internet addiction [108]. More recent studies have not shown an association with Internet-addictive behavior [114, 115];
- rs25531 (serotonin transporter (*SS-5HTTLPR*) gene, short allelic variants) – the research by Lee *et al*. [116] demonstrated that short allelic variants of the serotonin transporter gene might be associated with Internet addiction. Similar data were later obtained by Sun *et al*. but for men only [108]. As a large number of studies have shown, these genetic variants are also linked to a predisposition to depression, which is the most frequently detected comorbid condition among Internet-addictive individuals.

Recent studies revealed that a link between depression and autistic personality traits with generalized Internet addiction could be modulated by such polymorphism (5-HTTLPR/rs25531), as well as ethnic and geographic factors [115, 117].

- rs1044396 (nicotinic acetylcholine receptor subunit alpha 4 (CHRNA4) gene) – a small case-control study by Montag *et al.* [118] showed an association between Internet addiction and the rs1044396 CC genotype, which can also be associated with nicotine addiction and attention disorders.

  Later, Jeong *et al.* [119] conducted a pilot study of the target exome, involving 30 adults with addiction to computer games and 30 healthy individuals, which included a study of 72 candidate genes. This study showed a statistically convincing association with one site only – rs1044396. No such association was found in another study [114];
- rs2229910 (neurotrophic tyrosine kinase receptor type 3 (NTRK3) gene) – Kim *et al.* [120] have conducted in turn a pilot study of the target exome involving 30 adults with addiction to computer games and 30 healthy individuals, which included a study of 83 polymorphic sites. Their study also revealed a statistically convincing association with one site only – rs2229910, presumably also associated with anxiety-panic, depressive disorders, obsessive-compulsive disorder, and psychologically determined eating disorders;
- rs28364027 (Corticotropin Releasing Hormone Receptor 1 (CRHR1) gene) – a study involving Korean adolescent boys revealed that carriers of the AA genotype and the A allele were more predisposed to online computer games addiction [114]. It was previously determined that corticotropin-releasing hormone was involved in the mechanisms of negative effects realization when weaning from the addiction factor [121] and was associated with the risk of alcohol dependence for adolescents, especially when combined with stressful effects [122-124];
- rs1137070 (monoamine oxidase-A (MAOA) gene, EcoRV polymorphism) – the association of this polymorphism with an addiction to computer games with a mediator effect of hostility was evaluated for young adults. Participants with the TT rs1137070 genotype had a higher odds ratio of 2.52 (1.37–4.64) for gaming addiction compared to C allele carriers [125];

- rs2268498 (oxytocin receptor (OXTR) gene) – it has been shown that male carriers of the TT genotype (but not female) have lower levels of generalized Internet addiction compared to C allele carriers [126];
- rs6265 (*BDNF* gene) – Russian researchers discovered in 2019–2020 that genetic polymorphism of *BDNF* rs6265 (Val66Met), as well as the abovementioned *DRD4* exon 3 VNTR and *NTRK3* rs2229910, are were with the risk of generalized Internet addiction for young adults [127].

The latest (2022) review by Werling and Grünblatt [128] and the data presented in this article demonstrate that all currently known studies of genetic associations have been conducted for computer games addiction or (less often) for generalized Internet addiction. As far as is known, not a single study of genetic associations concerning PSMU has been published.

Discussion.

Neurobiology and genetics research on Internet-addictive behavior conducted over the last 10–15 years has allowed accumulating the necessary amount of knowledge to make certain intermediate conclusions, summarized recently in a significant number of meta-analyses and reviews. A large number of neuroimaging and neurophysiological studies have shown that Internet addiction is characterized by certain structural and functional features of the brain, accompanied by a significant violation of inhibitory control (increased impulsivity as a common factor in various forms of addictive behavior), stop-signal task, decision-making, and working memory. It has been discovered that, like other types of chemical and behavioral addictions, Internet addiction is characterized by an impairment of the metabolism of dopamine, serotonin, opioids, and some other neurotransmitters, which affects reward processing, executive functioning, salience attribution, and habit formation. A small number of pilot projects partially confirm the genetic basis of Internet addiction pathogenesis, previously demonstrated by twin studies.

An important aspect and trend in modern research on Internet-addictive behavior is an attempt to avoid the study of generalized, undifferentiated Internet addiction in favor of analyzing its specific forms, such as computer games addiction and PSMU [24, 129, 130]. At the same time, the vast majority of the mentioned neurobiological studies were

focused on computer games addiction (e.g. 85% of patients for functional magnetic resonance imaging [131]) and generalized Internet addiction (without taking into account the consumed content). Even though a certain number of neuroimaging studies have been conducted for PSMU [69], there is practically no research on neuropeptide and genetic associations for PSMU to date.

Although studies of generalized Internet addiction – especially for women – can be partially extrapolated to PSMU (taking into account common gender and psychosocial characteristics for some populations [24]), it is extremely important to study the directly verified PSMU, which differs significantly from computer games addiction. Additional research is needed to better identify common features and differences in the neurobiology for various types of addictive online behavior in the context of consumed content, devices, and technologies used (PCs, tablets, smartphones), as well as the stability of symptoms in the age aspect.

The study of neuropeptides directly involved in social bonding: oxytocin and vasopressin, as well as orexin, melatonin, and neurotrophic factors (BDNF and GDNF), looks promising for PSMU neuromolecular associations.

Genetic studies conducted on small samples, conflicting and still quite scarce, should also be expanded to specific forms of Internet addiction, such as PSMU and smartphone addiction [102]. Replication studies with a large number of participants are urgently needed, as well as genome-wide association and polygenic risk score estimate projects.

Conclusion.

In this narrative review, we discussed neurobiological risk factors for Internet addiction with a focus on current evidence on the association between PSMU and structural / functional characteristics of the brain and autonomic nervous system, neurochemical correlations, and genetic features. A review of the literature shows that the vast majority of the mentioned neurobiological studies were focused on computer games addiction and generalized Internet addiction (without taking into account the consumed content). Even though a certain number of neuroimaging studies have been conducted for PSMU, there is practically no research on neuropeptide and genetic

associations for PSMU to date. This fact points to the extremely high relevance of such studies.

Conflicts of Interest: The author declares no conflict of interest.

Abbreviations:

BDNF	brain-derived neurotrophic factor
CHRNA4	nicotinic acetylcholine receptor subunit alpha 4
CI	confidence interval
COMT	catecholamine-o-methyltransferase
CRHR1	corticotropin-releasing hormone receptor 1
DRD2	dopamine D2 receptor
DRD4	dopamine D4 receptor
GDNF	glial cell line-derived neurotrophic factor
I-PACE	Interaction of Person-Affect-Cognition-Execution
MAOA	monoamine oxidase-A
NTRK3	neurotrophic tyrosine kinase receptor type 3
OR	odds ratio
OXTR	oxytocin receptor
PIU	problematic Internet use
PSMU	problematic social media use
SDMS	Social Media Disorder Scale questionnaire

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The Second Round

SPECIFIC COMMENTS TO AUTHORS

SPECIFIC COMMENTS TO AUTHORS After modification, the structure and content of this paper have been improved, with comprehensive exposition and clear research objectives. But there are too many keywords. It is recommended to reduce to 3-5 keywords.

Response:

The number of keywords is reduced to 5: Internet addiction; Problematic social media use; Addictive behavior physiopathology; Neurobiology; Genetics The revised file is attached.