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Chapter 27

Molecular genetics of neurotransmitters and neuropeptides involved in Internet use disorders including first insights on a potential role of hypothalamus' oxytocin hormone

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Abstract

This chapter covers the phenomenon of Internet use disorders (IUDs) and putative associations with different neurotransmitter and neuropeptide systems. Genes coding for such messengers can be seen as an important starting point in the complicated quest to understand human behavior including new phenomena such as IUDs.

Therefore, a special focus of this chapter will lie on individual differences in molecular genetic underpinnings of neurotransmitter and neuropeptide systems and their associations with individual differences in tendencies towards IUDs. By shedding light on these associations, putative predisposing molecular genetic factors for the emergence and maintenance of IUDs can be carved out. Therefore, first an introduction to IUDs and a model that can guide research on putative associations of IUDs with different specific neurotransmitters and neuropeptides will be presented. Subsequently, twin studies on the heritability of IUDs are reviewed. Finally, studies on differences in molecular genetic predispositions and their associations with differences in IUDs will be presented and discussed, including targets related to the dopaminergic and serotonergic system as well as the hypothalamic neuropeptide oxytocin. The chapter closes with a conclusion about what is already known and what needs to be investigated in future studies to gain further insights into putative associations between molecular genetic markers and IUDs.

INTERNET USE DISORDERS

Internet use disorder (IUD), previously known for example as "Internet addiction" (Pontes et al., 2015) or "pathological Internet use" (Davis, 2001), has gained increasing attention in scientific research since the first case study published (Young, 1996). However, given the lack of an official diagnosis and hence of diagnostic criteria, there is no consensus on a definition. Nevertheless, in broad terms IUD could be seen as "excessive or poorly controlled preoccupations, urges, or behaviors regarding computer use and Internet access that lead to impairment or distress" (Weinstein et al., 2014, p. 99).

Several putative symptoms of an IUD are frequently debated. For example, Young (1998) used revised symptoms of gambling disorder to classify an IUD. As such, she constituted symptoms including preoccupation, tolerance, loss of control, withdrawal, risking social relationships or job/educational chances due to Internet use, lying to others about one's Internet use, and mood modification (Young, 1998). Similarly, Tao et al. (2010) suggested a "2 + 1 rule":

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while both preoccupation and withdrawal were defined as necessary symptoms to diagnose an IUD, at least one additional symptom of tolerance, loss of control/persistent desire to use the Internet, ongoing use of the Internet despite realizing negative consequences, loss of interest in other hobbies and activities, and mood regulation must be prevalent. Additionally, a functional impairment must be prevalent and the IUD must have lasted for at least 3 months with at least 6h of daily Internet usage, while the excessive Internet use should not be better explained by psychotic disorders or bipolar I disorder (Tao et al., 2010). Interestingly, to diagnose an IUD, many researchers emphasize the importance of negative consequences on one's life due to Internet use and differentiate between merely time-consuming/excessive use and IUD (Tao et al., 2010; Pontes et al., 2015).

In sum, the symptoms discussed in light of an IUD are partly overlapping with the symptoms of substance dependences (World Health Organization, 2019). However, it must be noted that the adoption of substance dependence symptoms to an IUD is often debated, and it is important to not overemphasize abnormality in everyday behavior (Billieux et al., 2015; Kardefelt-Winther et al., 2017). It is therefore important to note that an IUD is often seen as a dimensional construct from no/normal Internet use via problematic use to IUD (Tao et al., 2010; Montag et al., 2011; Müller et al., 2017; Sindermann et al., 2018). Among others due to the ongoing debate about the term, definition, and diagnostic criteria, prevalence rates vary between studies and between regions. A meta-analysis across 31 countries reported prevalence rates between 2.6% in Northern and Western Europe and 10.9% in the Middle East (Cheng and Li, 2014).

An important early model to explain the emergence and maintenance of an IUD is the *Cognitive-Behavioral Model of Pathological Internet Use* by Davis (2001) emphasizing maladaptive cognitions. More specifically, the model by Davis (2001) is a diathesis-stress model and is designed as a process model. Psychopathology such as depression can be seen as a diathesis. Stress can be caused by the discovery of the Internet or certain activities that can be carried out on the Internet (Davis, 2001). Other important components of the model to explain the emergence and maintenance of an IUD are rewarding effects of Internet use, lack of social support, and, importantly, maladaptive cognitions. In sum, an IUD is thought to be a consequence of maladaptive cognitions and behavioral responses that intensify or at least maintain maladaptive Internet use. Importantly, Davis (2001) was one of the first to differentiate between unspecified/generalized and specific IUDs. He proposed that unspecified IUD refers to pathologic overuse of the Internet in general. As such, unspecified IUD includes wasting time online with no clear objective. Specific IUDs, on the contrary, were defined as pathologic overuse of specific Internet activities and were seen as problems transferred from the offline to the online world, for example offline and online gambling (Davis, 2001).

Today, the separation of unspecified and specific IUDs is still important. Often the differentiation is illustrated between the specific IUDs of Internet gambling disorder, gaming disorder, buying-shopping disorder, communication/social networks use disorder, and pornography use disorder (Montag et al., 2015, 2020b; Brand et al., 2016; Müller et al., 2017; Sindermann et al., 2018). For now, only gambling and gaming disorder (predominantly online or offline) are official diagnoses in the International Classification of Diseases – 11th Revision (ICD-11) (World Health Organization, 2019). Of note, the term Internet use disorder is used throughout this chapter in order to strive for unification of terms in the literature, based on the terminology for gaming disorder used in the ICD-11.

To explain the emergence and maintenance of IUDs, currently the *Interaction of Person-Affect-Cognition-Execution model* (I-PACE) and its updated version are often considered as a relevant theoretic framework (Brand et al., 2016, 2019). The initial I-PACE model is an integration of various theoretic ideas and models and can be understood as a general model for specific IUDs. It is defined as a process model comprising temporal dynamics of the "addiction" process (Brand et al., 2016). As already indicated by the name of the model, it proposes complex mediating and moderating effects between personal (predisposing) factors and affective, cognitive, and executive functioning variables. Affective and cognitive factors comprise constructs such as coping mechanisms, cognitive biases, attentional biases, and the urge for mood regulation. Executive factors refer among others to inhibitory control mechanisms or lack thereof (Brand et al., 2016). Importantly, the personal/predisposing factors comprise not only social cognitions, personality, psychopathologies, and specific use motives, but also the biopsychological constitution of a person (Brand et al., 2016). The latter refers to genetic factors as well as ontogenetic aspects with regard to biologic systems.

The updated I-PACE model broadens the perspective and constitutes not only being applicable to specific IUDs but more broadly to general addictive behaviors, including unspecified IUD. Moreover, the updated I-PACE model differentiates between variables involved in addictive behaviors in general and variables involved only in specific addictive behaviors. It also differentiates between the mechanisms involved in the early and later stages of an "addiction" process. Finally, it goes more into detail with regard to what the authors call an "inner circle

of the addiction process" (Brand et al., 2019, p. 2), hence, explaining mediating and moderating effects in more detail based on recent literature (Brand et al., 2019). Of importance for the present chapter and without going into excessive detail: genetic factors are included in the I-PACE model as a person's core characteristics. Such characteristics are seen as important predisposing factors underlying various addictive behaviors, i.e., putatively unspecified as well as specific IUDs (Brand et al., 2019). Therefore the I-PACE model may be used as a basis to investigate molecular genetic underpinnings of unspecified and specific IUDs.

NEUROTRANSMITTERS, NEUROPEPTIDES, AND INTERNET USE DISORDERS

Within the broad topic of the emergence and maintenance of IUDs, this chapter focuses specifically on the role of molecular genetics associated with neurotransmitters and neuropeptides. Potential starting points to search for neurotransmitters/neuropeptides being associated with IUDs are manifold. For example, one can focus on neuropeptides which are known to be associated with behaviors and traits closely related to IUDs, such as the personality traits of low self-directedness, high impulsivity, low conscientiousness, and high neuroticism (all are related to unspecified IUD (Montag et al., 2010, 2011; Sariyska et al., 2014; Lachmann et al., 2017; Peterka-Bonetta et al., 2019)) or other addictive behaviors and substance dependences. However, this chapter will focus on a model, which is based on abundant neuroscientific research and directly deals with the topic of IUDs. Importantly, this model deals with unspecified IUD but results might also be transferrable to certain specific IUDs.

The model of interest by Montag et al. (2016) associates unspecified IUD with personality traits derived from the *Affective Neuroscience Theory*. Drawing on a large body of animal research, *Affective Neuroscience Theory* identifies seven systems in the mammalian brain; in detail, in evolutionary old, subcortical brain regions (Panksepp, 1998). Therefore these systems are likely to be conserved across the mammalian brain, hence, also found in the human brain (Maclean, 1985; Panksepp, 1998). As these systems influence emotionality in a bottom-up fashion, they are also known as primary emotional systems. These systems are labeled SEEKING, CARE, PLAYFULNESS, LUST, and FEAR, PANIC/GRIEF, and RAGE. Note that the primary emotional systems are written in capital letters based on the convention established for labeling neurologically based emotional primes (Davis et al., 2003).

While the first four primary emotional systems have a positive valence, the latter ones have a negative valence. As emotionality is an important part of personality, in humans six of these systems are measured as personality traits by means of the Affective Neuroscience Personality Scales (Davis et al., 2003; Davis and Panksepp, 2011; Reuter et al., 2017b). In detail, these six primary emotional traits are labeled SEEKING, CARE, PLAYFULNESS, FEAR, SADNESS (from the PANIC/GRIEF system), and ANGER (from the RAGE system) (Davis et al., 2003; Davis and Panksepp, 2011; Reuter et al., 2017b). LUST is not included in the questionnaire due to potential confounding effects and biases when answering questions on one's sexual behavior (Davis and Panksepp, 2011). Of major importance, due to abundant animal research and pharmacological challenge studies as well as electric brain stimulation studies, each of the primary emotional systems is linked to certain brain areas and neurotransmitters/neuropeptides (Panksepp, 1998, 2011). Therefore also in humans, the primary emotional traits are most likely linked to the brain areas and neurotransmitters/neuropeptides, which are linked to the respective primary emotional systems in mammals (for examples, see Table 27.1). Therefore, if primary emotional traits are associated with IUDs, IUDs might in turn be associated with the neurotransmitters/neuropeptides which are linked to the respective primary emotional system.

In a sample of $N = 680$ German-speaking participants, Montag et al. (2016) found that the overall unspecified IUD score was inversely associated with the positive primary emotional traits (SEEKING, CARE, PLAYFULNESS) and positively related to the negative primary emotional traits (FEAR, SADNESS, ANGER). Most pronounced associations were found for the associations with FEAR, SADNESS, and CARE (see regression analysis in the paper). These associations provide an important roadmap to the study of neurotransmitters/neuropeptides potentially associated with IUDs. For example, in Table 27.1, the underlying brain structures and neurotransmitters/neuropeptides associated with FEAR, SADNESS, and CARE, and therefore putatively also associated with unspecified IUD, are listed. As can be seen in this table, oxytocin is an important neuropeptide modulating the activity of the FEAR (downregulation), SADNESS (downregulation), and CARE (upregulation) circuitries. Given the links of higher FEAR, higher SADNESS, and lower CARE, with higher scores in unspecified IUD, oxytocin might be an important neuropeptide explaining the underlying biochemistry of unspecified IUD; and maybe also specific IUDs. In sum, based on the *Affective Neuroscience Theory* framework, oxytocin seems to be a promising candidate neuropeptide to study associations with IUDs (see Montag et al. (2016) for further information and more detailed explanations).

Table 27.1

Primary emotional traits/systems associated with the overall unspecified IUD score and their underlying brain neuroanatomy and neurotransmitters/neuropeptides

Primary emotional trait (system)	Brain neuroanatomy related to the system	Some neurotransmitters/neuropeptides related to the system
FEAR	Central and lateral amygdala to medial hypothalamus and dorsal periaqueductal gray	Glutamate (+), corticotropin-releasing factor/hormone (+), cholecystokinin (+), alpha-melanocyte-stimulating hormone (+), oxytocin (−)
SADNESS (PANIC/GRIEF)	Anterior cingulate, bed nucleus of stria terminalis and preoptic area, dorsomedial thalamus, periaqueductal gray	Opioids (−), oxytocin (−), prolactin (−), corticotropin-releasing factor/hormone (+), glutamate (+)
CARE	Anterior cingulate, bed nucleus of stria terminalis, preoptic area, ventral tegmental area, periaqueductal gray	Oxytocin (+), prolactin (+), dopamine (+), opioids (+/−)

Table content based on Montag C, Sindermann C, Becker B et al. (2016). An affective neuroscience framework for the molecular study of internet addiction. Front Psychol 7. https://doi.org/10.3389/fpsyg.2016.01906 and Montag C, Davis KL (2018). Affective neuroscience theory and personality: an update. Personal Neurosci 1. https://doi.org/10.1017/pen.2018.10.
Note: + excitatory effects; − inhibitory effects.

TWIN STUDIES—ARE INTERNET USE DISORDERS HERITABLE?

As mentioned among others in the I-PACE model (Brand et al., 2016, 2019), genetic underpinnings are seen as important predisposing variables for the emergence of IUDs. Moreover, the model by Montag et al. (2016) provides further insight into which specific neurotransmitters/neuropeptides might underly IUDs. Combining the two approaches leads to a roadmap on which molecular genetic variables can be investigated for putative associations with IUDs. However, before going into detail, one first needs to check whether IUDs show a heritable component. Therefore twin studies are of utmost importance to examine how much variance in IUDs can be accounted for by genetic factors.

Many variables, for example, personality traits, which are known to be associated with IUDs, have been found to have a heritable component (Bezdjian et al., 2011; Polderman et al., 2015; Vukasović and Bratko, 2015; Hahn et al., 2017). However, instead of explaining these studies in detail, we will focus on twin studies explicitly investigating the heritability of IUDs. Of note, the twin studies available to date all deal with unspecified IUD.

In a sample of $N = 237$ Turkish twin pairs, both additive genetic effects and nonshared environmental effects each explained about 42% of the variance in unspecified IUD, whereas the shared environment accounted for only about 17%. However, genetic effects were only prevalent in men but not in women according to comparisons of monozygote and dizygote twin correlations (Deryakulu and Ursavaş, 2014). In a sample of $N = 825$ twin pairs from China, Li et al. (2014) found that in women around 58% of the variation in unspecified IUD could be explained by genetic effects and in men around 66%. The remaining variation could be explained by nonshared environmental factors. Moreover, in a sample of $N = 5247$ twins from the Netherlands, it was found that in men and women equally, around 48% of the variation in unspecified IUD was explained by genetic factors while the remaining variation was explained by nonshared environmental factors (Vink et al., 2016). Another twin study on $N = 355$ twin pairs from Germany found that genetic effects did not explain a significant amount of variation in overall unspecified IUD scores (Hahn et al., 2017). Nonshared and shared environmental factors did explain a significant amount of variation. However, for specific subfacets of unspecified IUD, such as loss of control, mood regulation, and negative outcomes, heritability was estimated to lie between 21% and 33% (Hahn et al., 2017).

In sum, these twin studies suggest that part of the variance in unspecified IUD can be accounted for by genetic factors. A roadmap for which specific genetic factors might influence the susceptibility for unspecified IUD can be found in the model by Montag et al. (2016) and has been mentioned earlier. Initial results of molecular genetic association studies are detailed in the next paragraph.

INITIAL MOLECULAR GENETIC FINDINGS IN THE LIGHT OF INTERNET USE DISORDERS

This paragraph deals with individual differences in molecular genetic factors and how these differences might influence the risk for vs resilience against the emergence

of IUDs. Various genetic association studies exist, which link individual differences in molecular genetic variables to individual differences in psychologic constructs known to be associated with IUDs (such as personality traits (Okbay et al., 2016; Lo et al., 2017; Gray et al., 2018; Hennig et al., 2020)). These studies might further provide insight into putative molecular genetic factors associated with IUDs. Nevertheless, this part of the chapter will focus on initial studies directly linking individual differences in molecular genetic factors to differences in IUDs. In line with our approach throughout the chapter, we will review studies on unspecified IUD. However, also several studies on Internet gaming disorder have been conducted (according to ICD-11 nomenclature: gaming disorder, predominantly online; we use the term "Internet gaming disorder" to use the term "disorder" consistently throughout the chapter; we do not apply the ICD-11 nomenclature due to the fact that none of the studies investigated the disorder against the background of the ICD-11 framework). We will therefore also review these studies in this part of the chapter.

Molecular genetic underpinnings of neurotransmitter systems

Molecular genetic underpinnings of the dopamine system

One of the first studies investigating the molecular genetic underpinnings of an IUD compared the distributions of alleles in two dopaminergic polymorphisms between 79 men classified as suffering from Internet gaming disorder and 75 age- and gender-matched control participants from South Korea (Han et al., 2007). The two polymorphisms of interest were the dopamine receptor D2/ankyrin repeat and kinase domain containing 1 (DRD2/ANKK1) Taq1A (rs1800497) single nucleotide polymorphism (SNP) and the catechol-*O*-methyltransferase (COMT) Val158Met (rs4680) SNP (Han et al., 2007). The DRD2/ANKK1 Taq1A genotypes seem to be associated with differences in the DRD2 binding (potential); A2/A2 homozygotes show a higher binding (potential) than A1+ carriers (A1/A2, A1/A1) (Gluskin and Mickey, 2016; Tunbridge et al., 2019). In the study by Han et al. (2007), both the A1/A2 and A1/A1 genotypes of the DRD2-Taq1A SNP were more prevalent in the group of participants with Internet gaming disorder compared to the control group. Therefore the A1 allele associated with lower D2 receptor binding (potential) seems to be positively associated with Internet gaming disorder, hence, maybe also unspecified IUD and other specific IUDs. Interestingly, the same allele (A1) has also been associated with a risk for alcohol, smoking, and opioid dependence (Munafò et al., 2007; De Ruyck et al., 2010; Wang et al., 2013a,b; Deng et al., 2015).

The COMT Val158Met SNP causes a valine to methionine substitution in the 158th codon of the COMT gene, thereby moderating the dopamine catabolism by the COMT enzyme in the synaptic cleft. In more detail, the Val allele is associated with higher enzyme activity, hence, higher dopamine catabolism (Lachman et al., 1996; Chen et al., 2004; Tunbridge et al., 2019). Of importance, the mechanism of varying COMT enzyme activity is potentially of major importance in the prefrontal cortex due to a paucity of dopamine transporters in this region (Sesack et al., 1998; Lewis et al., 2001). In the study by Han et al. (2007), the Met allele of the COMT Val158Met SNP occurred more frequently in the Internet gaming disorder group compared to the control group but only when comparing Met+ (Met/Met + Val/Met) vs Met- (Val/Val) carriers. This finding indicates that the allele associated with lower enzyme activity and lower dopamine catabolism is positively associated with Internet gaming disorder.

Aside from the study by Han et al. (2007), another study could not confirm the role of the DRD2/ANKK1 Taq1A SNP in Internet gaming disorder in a sample of 63 subjects with Internet gaming disorder and 87 control subjects from South Korea (Paik et al., 2017). Moreover, no association between Internet gaming disorder and a DRD2 SNP (rs6277) was found (Paik et al., 2017). However, associations between the -141C insertion/deletion (Ins/Del) polymorphism and certain symptoms of Internet gaming disorder in men were observed: In men, the group of participants carrying the Del- genotype (Ins/Ins) showed a higher prevalence of symptoms of "continued excessive use of Internet games despite knowledge of psychosocial problems" and "mood modification" (Paik et al., 2017, p. 4). This polymorphism is perhaps associated with DRD2 gene expression with lower expression associated with the Del allele; however, findings are mixed (Arinami et al., 1997; Pohjalainen et al., 1999). On a psychologic level, the Ins allele of this polymorphism might be associated with alcohol dependence, but—again—results are mixed (Ishiguro et al., 1998; Sander et al., 1999; Parsian et al., 2000; Konishi et al., 2004; Prasad et al., 2010). Additionally, the polymorphism has mostly been studied in the context of schizophrenia, although the associations are not clear, yet (Ohara et al., 1998; Glatt et al., 2004).

Another study on the associations between dopamine-related polymorphisms and unspecified IUD investigated the associations between the COMT Val158Met (rs4680; see previously mentioned) and rs4818 SNPs (Ioannidis et al., 2020). The sample consisted of 206 individuals from the United States, 24 classified as suffering from an unspecified IUD and 182 not suffering from an IUD. For none of the polymorphisms under investigation, an association with unspecified IUD was found (Ioannidis et al., 2020).

In summary, there is indication that dopamine-related genetic polymorphisms might be associated with individual differences in Internet gaming disorder, hence, potentially also with other specific IUDs and/or unspecified IUD. This is also in line with the *Affective Neuroscience Theory* framework by Montag et al. (2016), which indicates dopamine as a putative neurotransmitter associated with IUDs, because both (unspecified IUD and dopamine) are associated with CARE. Moreover, dopamine is important for the SEEKING system (Panksepp, 2011), which without a doubt plays an important role in addiction, although no associations could be observed with unspecified IUD in the Montag et al. (2016) work, probably due to suboptimal operationalization of the SEEKING items in the context of an addiction framework. However, despite theoretical support for the associations between IUDs and dopamine-related genetic polymorphisms, the failed replications of molecular genetic findings between studies as reported previously need to be considered.

Molecular genetic underpinnings of the cholinergic system

In this section, we will focus on the nicotinic acetylcholine receptor gene subunit alpha 4 (CHRNA4). This is an interesting candidate gene in the study of IUDs, among others, because it is indirectly related to the dopaminergic system (Parish et al., 2005; Markett et al., 2009, 2011).

Montag et al. (2012) investigated the allelic distributions of a SNP (rs1044396) in the CHRNA4 gene between 132 German individuals categorized with an unspecified IUD vs gender- and age-matched controls. Montag et al. (2012) found that the homozygous CC genotype occurred more frequently in the group suffering from unspecified IUD, an effect driven by women. Of major interest, this result could in part be replicated with regard to Internet gaming disorder. A study by Jeong et al. (2017) in a sample of 30 men with Internet gaming disorder and 30 gender-matched controls from South Korea found that the T allele occurred less often in the Internet gaming disorder group. Additionally, the CC genotype carriers showed higher scores in the Internet gaming disorder scale compared to T+ carriers (TT+CT). This indicates that while the T allele seems to be protective, the C allele (especially the homozygote CC genotype) seems to be associated with a higher risk for Internet gaming/use disorder. Of importance, the C allele of this SNP might also be associated with a higher risk for nicotine dependence (Feng et al., 2004). Finally, it needs to be noted that a total of 72 individual genes were investigated in the study by Jeong et al. (2017), but only the effect of the CHRNA4 rs1044396 SNP was significant after (genomic-control) correction.

These findings underline the importance of the CHRNA4 gene in IUDs but might also strengthen the role of dopamine in IUDs given the putative interactions between the two systems (Parish et al., 2005; Markett et al., 2009, 2011).

Molecular genetic underpinnings of the serotonin system

In addition to dopamine-related polymorphisms, also a prominent polymorphism of the serotonin system has been investigated in light of IUDs.

A study by Lee et al. (2008) compared the distributions of different alleles in 5-HTTLPR in a sample of 91 men classified with an unspecified IUD and 75 men as control subjects from South Korea. 5-HTTLPR is a polymorphism in the promotor region of the serotonin transporter gene (SLC6A4) comprising a short and/or a long allele. The long allele shows a higher gene expression rate than the short allele (Lesch et al., 1996). Lee et al. (2008) found in their study that the homozygous short/short genotype was more prevalent in individuals categorized with unspecified IUD. Of note, 5-HTTLPR has been investigated in the context of many psychiatric disorders and might also be associated with alcohol dependence. However, results are difficult to interpret due to putative publication bias in the published results and methodological issues such as small sample sizes (McHugh et al., 2010; Kenna et al., 2012).

Nevertheless, this finding indicates that differences in the serotonin system might be of importance to explain the emergence and maintenance of IUDs.

Molecular genetic underpinnings of neuropeptide systems

Molecular genetic underpinnings associated with the corticotropin-releasing hormone

Park et al. (2018) investigated polymorphisms associated with various neurotransmitter/neuropeptide systems in a sample of 118 men with Internet gaming disorder and 112 men without Internet gaming disorder from South Korea. Specifically, the dopamine receptor D4 variable number of tandem repeat (VNTR) polymorphism, the dopamine transporter 1 VNTR polymorphism, a noradrenaline transporter/norepinephrine 8 polymorphism (rs5569), the CHRNA4 SNP (rs1044396; see previously mentioned), and a corticotropin-releasing hormone receptor 1 SNP (CRHR1) (rs28364027) were investigated. Only the CRHR1 SNP exhibited a significant difference between the Internet gaming disorder and control groups. In more detail, the AA genotype occurred more

frequently in the group of individuals with Internet gaming disorder. This finding is of great interest as CRH is associated with FEAR and SADNESS according to the *Affective Neuroscience Theory*, hence, potentially also to (unspecified) IUD according to the molecular genetic framework by Montag et al. (2016). Moreover, it is interesting to note that other polymorphisms of the CRHR1 gene have been associated with symptoms of disorders such as alcohol dependence, potentially in conjunction with stressful or adverse life events (Treutlein et al., 2006; Blomeyer et al., 2008; Chen et al., 2010; Glaser et al., 2014).

Molecular genetic underpinnings of the oxytocin system

One study investigating the link between a functional oxytocin receptor (OXTR) gene SNP (rs2268498) and real-world behavior tracked via a smartphone should be mentioned. The rs2268498 is located in the promoter flanking region of the OXTR gene and the T allele (vs the C allele) is associated with lower OXTR mRNA expression on the biologic level (Reuter et al., 2017a) and with higher scores in face recognition (Melchers et al., 2013), interpersonal perception (Melchers et al., 2015), and empathic concern (a subfacet of empathy; TT vs TC and CC) (Christ et al., 2016) as well as lower autistic tendencies (especially for TT-genotype carriers) (Montag et al., 2017) on a psychologic level.

Despite not investigating IUD specifically, this particular study should be mentioned because it (i) investigates a polymorphism related to the oxytocin system, which might be associated with (unspecified) IUD according to the framework by Montag et al. (2016), and (ii) points toward a new line of research objectively investigating real-world variables instead of self-report measures in association with molecular genetics.

In a sample of 117 German participants, the study by Sariyska et al. (2018) found that the TT-genotype of rs2268498 was linked to a higher number of active contacts (the average number of contacts a participant was in contact with per day through phone calls) and a higher number of incoming calls compared to C+ carriers (CC+CT). Results were weaker when age was taken into account. This finding indicates that the T allele (especially the homozygous TT genotype), generally being associated with more prosocial tendencies, is also associated with greater social use of the smartphone. Nevertheless, whether rs2268498 is associated with the "addictive" use of the smartphone or its communication applications (i.e., a mobile version of IUD) needs to be clarified in future studies. The study by Sariyska et al. (2018) "only" points toward an association with greater social use, but not necessarily also "addictive" use. Importantly, a conference abstract exists which points toward a protective effect of the TT genotype in rs2268498 against unspecified IUD (Sariyska et al., 2016).

Further findings on putative molecular genetic underpinnings

In addition to the prominent polymorphisms from the neurotransmitter/neuropeptide systems mentioned previously, some other polymorphisms have been investigated in light of IUDs.

A study by Kim et al. (2016) investigated various genetic variants in 30 men with Internet gaming disorder and 30 men as control participants from South Korea. More specifically, targeted exome sequencing was used to investigate 159 genes and 83 SNPs, which were putatively associated with Internet gaming disorder. Of all variants under investigation, only one SNP—rs2229910 of the neurotrophic tyrosine receptor kinase, type 3 (NTRK3) gene—showed a significant association with Internet gaming disorder after adjustment of *P*-values. In detail, while the C allele was associated with a protective effect against Internet gaming disorder, the G allele was linked to a higher risk for Internet gaming disorder (Kim et al., 2016). The gene on which this SNP lies (NTRK3) codes for a receptor of the neurotrophic tyrosine kinase (NTRK) family (https://www.ncbi.nlm.nih.gov/gene/4916). The roles of this gene and this specific SNP on psychologic variables are not well studied, yet. Therefore the role of this polymorphism in Internet gaming disorder needs further clarification.

CONCLUSION

Despite most IUDs not being an official diagnosis, yet—except for the related gambling and gaming disorders in the ICD-11 (World Health Organization, 2019)—a great deal of research on this topic was conducted throughout the past years. Nevertheless, studies on the molecular genetic basis of IUDs are rare. Only eight studies (and one conference abstract) investigating mostly different genetic polymorphisms in light of IUDs could be identified. These studies mostly deal with various neurotransmitter systems such as the dopaminergic or the serotonergic system and neuropeptides. A summary of the studies can be found in Table 27.2.

Overall, the studies reviewed in this chapter have certain limitations, which make it difficult to draw a clear conclusion. First of all, most of the studies consist of rather small sample sizes of individuals classified as

Table 27.2

Overview of the genetic polymorphisms putatively linked to unspecific IUD and/or Internet gaming disorder according to previous studies

Gene	Associated with neurotransmitter/ neuropeptide/brain molecule	Polymorphism	References
Related to neurotransmitter systems			
Dopamine receptor D2 (DRD2)/ ANKK1	Dopamine	Taq1A/ rs1800497	Han et al. (2007) (Paik et al., 2017)
Catechol-O-methyltransferase (COMT)	Dopamine	Val158Met/ rs4680	Han et al. (2007) (Ioannidis et al., 2020)
Dopamine receptor D2 (DRD2)	Dopamine	-141C Ins/Del	Paik et al. (2017)
Nicotinic acetylcholine receptor subunit alpha 4 (CHRNA4)	Acetylcholine (dopamine)	rs1044396	Montag et al. (2012) Jeong et al. (2017) (Park et al., 2018)
Serotonin transporter (SLC6A4)	Serotonin	5-HTTLPR (short vs long variant)	Lee et al. (2008)
Related to neuropeptide systems			
Corticotropin-releasing hormone receptor 1 (CRHR1)	Corticotropin-releasing hormone/ factor	rs28364027	Park et al. (2018)
Oxytocin receptor (OXTR)	Oxytocin	rs2268498	Sariyska et al. (2016) (Sariyska et al., 2018)
Others			
Neurotrophic tyrosine kinase receptor, type 3 (NTRK3)	Neurotrophin 3	rs2229910	Kim et al. (2016)

Note: References in parentheses indicate studies that found nonsignificant associations between IUD and the specific polymorphism. The study by Sariyska et al. (2018) did not specifically investigate IUD but only the use of the smartphone.

suffering from an IUD, i.e., between 24 (Ioannidis et al., 2020) and 132 participants (Montag et al., 2012). Clearly, these numbers, especially the latter one, can be considered high when taking into account the putative clinical context of an IUD. However, in light of molecular genetic association studies, where effect sizes are generally estimated to be very low, these sample sizes are still rather small. Therefore nonsignificant findings in some studies might be due to the low statistical power. Additionally, whereas some studies deal with unspecified IUD (Lee et al., 2008; Montag et al., 2012; Ioannidis et al., 2020), several other studies deal with Internet gaming disorder, specifically (Han et al., 2007; Kim et al., 2016; Jeong et al., 2017; Paik et al., 2017; Park et al., 2018), which hampers an overall generalization of results.

Moreover, the diagnostic criteria applied to diagnose an IUD/Internet gaming disorder vary between studies, further limiting generalizability. Next, the studies were implemented either in Korea (Han et al., 2007; Lee et al., 2008; Kim et al., 2016; Jeong et al., 2017; Paik et al., 2017), Germany (Montag et al., 2012; Sariyska et al., 2018), or the United States (Ioannidis et al., 2020) and hence also cultural aspects might have influenced the associations between genetics and IUDs, which could explain some of the differences between studies (Feldman and Laland, 1996; Kim et al., 2011).

Additionally, the genotypes of various polymorphisms under investigation are differently distributed between European and Asian samples (e.g., https://www.ncbi.nlm.nih.gov/snp/rs1800497#frequency_tab; https://www.ncbi.nlm.nih.gov/snp/rs4680#frequency_tab; https://www.ncbi.nlm.nih.gov/snp/rs1044396#frequency_tab), and this impacts statistical power when certain genetic variants occur more seldom or more often in a given population. At the same time, the different cultural backgrounds in conjunction with a nonreplication of findings make it hard to judge whether nonreplicated results between studies are due to different cultural backgrounds or because effects really do not exist.

All of these disadvantages make it hard to draw a final conclusion about which molecular genetic factors are really associated with IUDs/Internet gaming disorder and which are not. The only exceptions are the studies by Montag et al. (2012) and Jeong et al. (2017), which found the same molecular genetic variant (CHRNA4 rs1044396, C allele) to be associated with unspecified IUD and Internet gaming disorder in samples from Germany and South Korea. However, this association could not be replicated in a third study by Park et al. (2018).

In conclusion, some initial findings on molecular genetic factors underlying IUDs are available. These findings should guide further research on this topic. However, clearly much more research with much larger samples is necessary to replicate and/or test the robustness of these previous findings. Promising candidate neurotransmitters/neuropeptides seem to be related to the dopaminergic and cholinergic systems, among others. As we have outlined in the realm of *Affective Neuroscience Theory*, oxytocin might also be an interesting molecule to be studied in the context of IUDs. In addition to testing the robustness of previous findings, we also need to better understand why certain polymorphisms of different systems might be linked to IUDs (see, for example an association with the NTRK3 gene (Kim et al., 2016)). Finally, we are of the opinion that IUDs should be further investigated with a genome-wide-based approach, something which (i) would shed light on heritability estimates from a molecular perspective and (ii) would yield perhaps new genetic candidate markers to be investigated in the context of IUDs (for recent research strategies in the study of molecular genetics of individual differences, see Montag et al., 2020a).

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