

ANHEDONIA IN SCHIZOPHRENIA: MINI-REVIEW

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SUMMARY

The perception of reward exerts a powerful influence on human behavior. While anhedonia might occur in healthy individuals, its prevalence and severity are much higher in psychiatric patients, particularly those with depression and schizophrenia. Anhedonia is a negative symptom, and presumably a trait marker in schizophrenia. Recent research confirmed that anhedonia is a complex construct, consisting of anticipatory, consummatory, and reward learning components. In general, schizophrenia patients show anticipation deficits, and a substantial portion of them have physical (PA) and social anhedonia (SA). The relationship between anhedonia and psychopathology appears bidirectional. While gene-environment interactions affect reward circuitry, anhedonia modulates clinical features, such as suicidality and nicotine consumption. Future clinical research employing longitudinal designs may shed more light on the dynamics and treatment of anhedonia in schizophrenia.

Key words: anhedonia – schizophrenia - negative symptoms - suicidality

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INTRODUCTION

Anhedonia is usually defined as the diminished capacity to experience pleasure from otherwise pleasurable experiences. Numerous research, however, revealed a complex nature of this domain, since it comprises of several deficits in reward perception (processing). Actually, the pleasure cycle involves wanting (appetitive, anticipatory or motivational phase), liking (consummatory phase), and learning (satiety phase) (Craske et al. 2016).

Therefore, based on the latest findings, anhedonia should not be simply considered as a "loss of ability to experience pleasure" (Zhang et al. 2016), and a new definition was proposed, as an "impairment in the ability to pursue, experience, and/or learn about pleasure" (Thomsen 2015). It refers to a deficit of positive affect and involves a loss of desire or motivation to engage in the pleasurable activities (anticipatory anhedonia) and a loss of enjoyment in the pleasurable activities (consummatory anhedonia) (Craske et al. 2016). Also, Chapman et al. (1976) defined two different types of the hedonic deficit: physical anhedonia (PA) and social anhedonia (SA), which were extensively investigated in different clinical and non-clinical samples. While PA represents an inability to feel physical pleasure (such as eating, touching, and sex), SA describes an incapacity to experience interpersonal pleasure (such as being with and talking to others) (Chapman et al. 1976). Importantly, there was a strong correlation among social, physical, anticipatory, and consummatory anhedonia, as well as anhedonia measured by Snaith–Hamilton Pleasure Scale (Fortunati et al. 2015).

ANHEDONIA ACROSS PSYCHIATRIC DISORDERS

Reward is important for survival and procreation, while anhedonia is considered evolutionary maladaptive (Rømer Thomsen et al. 2015). Namely, anhedonia was recognized as a transdiagnostic feature more than 40 years ago, when it was found to be more prominent in chronic than in acute patients (Harrow et al. 1977). More recently, it became well-established that anhedonia might occur in any population (Ducasse et al. 2018), but it is more prevalent in patients with psychiatric disorders, such as depression, schizophrenia, personality disorders, substance-abuse disorders (Ducasse et al. 2018) and post-traumatic stress disorder (Nawijn et al. 2015). Likewise, a common pattern of large-scale network dysconnectivity was associated with reward deficits across clinical diagnostic categories, including major depressive disorder (MDD), bipolar disorder, schizophrenia, psychosis risk and healthy controls (Sharma et al. 2017).

Importantly, the characteristics of anhedonia differ across disorders. Patients with schizophrenia have deficits in anticipatory, but not consummatory reward (Yan et al. 2018), whereas individuals with depression experience deficits in anticipatory, consummatory and cognitive constituents (Fortunati et al. 2015, Lambert et al. 2018). In addition, a recent meta-analysis of controlled studies of anhedonia in either patient with schizophrenia or depression vs. control groups, reported larger deficits in anticipatory pleasure in patients with depression than in schizophrenia spectrum disorders (Hallford & Sharma 2019). These findings suggest the common deficits in

anticipatory anhedonia in both patients with schizophrenia and depression, although at different magnitudes (Hallford & Sharma 2019). Along with quantitative, qualitative differences in anhedonia might also exist between patients with MDD and schizophrenia (Lambert et al. 2018).

ANHEDONIA AND SCHIZOPHRENIA

There is growing evidence that schizophrenia is associated with an anticipatory pleasure deficit, such that individuals with the disorder anticipate less pleasure from future activities than healthy controls, resulting in a decrease in the goal-directed activities (see Watson & Naragon Gainey 2010). On the contrary, and for some authors surprisingly, individuals with schizophrenia displayed a normal capacity to experience pleasure in response to positive stimuli (Watson & Naragon Gainey 2010) and had levels of consummatory anhedonia similar to healthy controls (Fortunati et al. 2015). This dissociation between consummatory and anticipatory pleasure is referred to as „anhedonia paradox“, and is considered specific for schizophrenia. Due to the anticipatory anhedonia, individuals with schizophrenia might distance themselves from social contacts. SA is correlated with anxiety and social dysfunction in schizophrenia (Cieslak et al. 2015). Therefore, predominantly anticipatory anhedonia in schizophrenia is a part of „avolition-apathy“ domain, particularly in patients who are not depressed. In patients with schizophrenia, only anticipatory anhedonia was correlated with the same electrophysiological markers as avolition-apathy, suggesting different patterns of correlation for anticipatory and consummatory anhedonia (Giordano et al. 2018). Another difference between schizophrenia and other disorders, such as depression, is that it is associated with a reduced capacity to express their feelings (Watson & Naragon Gainey 2010).

ANHEDONIA THROUGHOUT THE DISEASE COURSE

The question is when do patients start to experience anhedonia? Individuals with ultra-high risk for psychosis, and those with recent-onset schizophrenia had higher scores of revised Physical Anhedonia Scale and Social Anhedonia Scales than healthy controls (Jhung et al. 2018). Anhedonia was reported to be a marker of increased risk for schizophrenia and a trait marker of the disease. First-degree relatives of patients with schizophrenia had higher scores of PA than the control group (Seidman et al. 2016). In addition, the prevalence of anhedonia was high in the first-episode patients, whose first psychotic symptoms appeared no longer than 14 days ago (an der Heiden et al. 2016). In fact, the presence of anhedonia has steadily decreased during the first years, followed by a plateau after 5 years, which persisted there after (an der Heiden et al. 2016). These presumptions suggest a genetic link between anhedonia and schizophrenia.

Extensive research consistently reported, with a large effect-size, higher scores of SA and PA in individuals with schizophrenia compared to healthy controls (see Watson & Naragon Gainey 2010, Cieslak et al. 2015, Fortunati et al. 2015, Eisenstein et al. 2017), while more than 60% of patients had moderate to severe scores of both anticipatory and consummatory anhedonia (Giordano et al. 2018). Anhedonia did not correlate with the duration of illness in schizophrenia (Li et al. 2015). Another study reported that PA was stable in schizophrenia for even 10 (Herbener & Harrow 2002) and 13 (Loas et al. 2009) years, respectively. Importantly, SA remained elevated in patients with schizophrenia during a one-year follow-up, while in depression, it returned to values similar to those in healthy individuals (Blanchard et al. 2001). These findings suggest that anhedonia might be less responsive to treatment in schizophrenia than in depression. Patients with anhedonia might be distinguished from those without it by high scores in the disorganization and negative dimensions (Pelizza & Ferrari 2009).

ANHEDONIA AND SUICIDALITY

In a recent meta-analysis of studies on different psychiatric and non-psychiatric populations, overall 20 subgroups, anhedonia was robustly associated with suicidality (Ducasse et al. 2018). Despite the well-determined relationship between suicidality and anhedonia in depression (Zimmerman et al. 2018), the research regarding anhedonia and suicidality in schizophrenia is sparse. Current suicidality correlated with PA, while a similar trend was obtained for SA (Kollias et al. 2008). Importantly, one study reported higher scores on PA (SA was not measured) in schizophrenia patients who committed suicide during 14-years follow-up, relative to patients who died from other causes (Loas et al. 2009). Given that anhedonia was both a trait marker in schizophrenia and associated with current suicidality irrespective of the presence of depression (Ducasse et al. 2018), it would be intriguing to investigate the association between anhedonia and life-time suicidal behavior, such as suicide attempts.

ANHEDONIA AND NICOTINE DEPENDENCE

The results of the majority of studies addressing anhedonia in schizophrenia did not measure smoking behavior (Blanchard et al. 2001, Kollias et al. 2008, Loas et al. 2009, Pelizza & Ferrari 2009, Cieslak et al. 2015, Fortunati et al. 2015, Li et al. 2015, an der Heiden et al. 2016, Jhung et al. 2016). However, both anhedonia and nicotine dependence are related to reward system dysfunction. While anhedonia might result from the hypodopaminergic state (Gold et al. 2018), individuals might smoke to increase dopamine levels in the reward system. For example, animal studies have reported that

nicotine elevated dopamine levels in nucleus accumbens (Zhang et al. 2018). Preclinical data emphasized the role of early adversity on both reward-related brain circuits and anhedonia-like behavior (Bolton et al. 2018). Early life-stressors are common in MDD and schizophrenia and might contribute to the development of anhedonia in these patients. The neural circuitry implicated in addictive drug use, which appears to be down-regulated in early abstinence, corresponds closely with brain reward pathways. Although patients with schizophrenia have the highest prevalence of smoking (see Sagud et al. 2018), the relationship between anhedonia and nicotine dependence was explored mainly in non-clinical populations. Nicotine ameliorated anhedonia in smokers without current psychiatric condition after the overnight abstinence (Powell et al. 2004). Another study in community members without current psychiatric diagnosis reported that nicotine enhanced positive affective response to mood induction only in individuals with anhedonia, while denicotinized cigarettes had no effect, which might explain strong cigarette craving in subjects with anhedonia (Cook et al. 2007). Although anhedonia was not associated with the number of cigarettes smoked daily, it was related to a greater frequency of past cessation attempts (Levenhal et al. 2009). There is also evidence that blunted reward responsivity relates to increased nicotine craving, at least in non-clinical populations (Peechatka et al. 2015).

To the best of our knowledge, only one study investigated anhedonia and smoking in schizophrenia, and reported the association between anhedonia and increased smoking behavior among smokers with schizophrenia, but not in control smokers (Anhallen et al. 2012). There is also evidence on the association between life-time regular cannabis use and decreased anticipatory pleasure in patients with schizophrenia (Schnakerberg & Lysaker 2019).

BIOLOGY OF ANHEDONIA

While the pleasure cycle involves wanting (appetitive, anticipatory or motivational phase), liking (consummatory phase) and learning (satiety phase), these components are proposed to have different neuronal substrates. For example, the dopaminergic system is involved in motivation and learning, whereas opioid, serotonergic and endocannabinoid system in the ventral striatum and orbitofrontal cortex are likely involved in consummatory reward (see Craske et al. 2016). The structure involved in motivational pleasure is the ventral tegmental area (VTA). When stimulated it increases the activation of the ventral striatum and behavioral drive (Ferenczi et al. 2016). A meta-analysis reported that consummatory anhedonia was associated with decreased activation in ventral basal ganglia areas, while anticipatory anhedonia was associated with more substrates in the frontal-striatal networks except for the ventral striatum (Zhang et al. 2016), with the central

role of nucleus accumbens, a region critical for reward processing (Sharma et al. 2017). Anhedonia is considered to result from the interaction of genetic variations and epigenetic alterations in response to environmental influences (Gold et al. 2018).

There is evidence for similarities in the biology of anhedonia in different psychiatric disorders, such as an overlap in the neural substrates of anhedonia between depression and schizophrenia (Zhang et al. 2016). More specifically, a common pattern of large-scale network dysconnectivity associated with reward deficits was observed across clinical diagnostic categories, such as in patients with schizophrenia, individuals at genetic or clinical high risk for psychosis, patients with MDD or bipolar disorder (Sharma et al. 2017). Likewise, reduced activation in the orbitofrontal cortex, ventral striatum, inferior temporal gyrus, and occipital cortex was observed in both depression and schizophrenia relative to processes in healthy participants during the receipt of unexpected reward, which suggests overlapping hypo-function in those regions in the two disorders (Segarra et al. 2016). Nonetheless, some differences were also observed. For example, reduced ventral striatal activity was related to greater anhedonia and overall depressive symptoms in the schizophrenia group, but not in participants with depression (Arrondo et al. 2015).

Given that dopamine plays a critical role in the feelings of pleasure associated with rewards, anhedonia is considered to involve the dysfunction of dopamine neurotransmission in reward circuitry (Ferenczi et al. 2016, Bolton et al. 2018, Gold et al. 2018). Therefore, functional polymorphisms of different components of the dopaminergic system might be expected to affect hedonic capacity. Given the frequent occurrence of anhedonia in the 22q11.2 deletion syndrome (Demily & Franck 2016), Catechol-O-methyltransferase (COMT) polymorphisms are studied in anhedonia. Several dopamine-related polymorphisms the dopamine D2 gene in the ankyrin repeat and kinase domain containing 1 (DRD2/ANKK1) gene (DRD2/ANKK1 TaqIA (rs1800497), COMT val158met (rs4680), the 48 bp exon 3 variable tandem number repeat (VNTR) polymorphism in the Dopamine D4 receptor gene, and the 40 bp the dopamine active transporter 1 gene (DAT1, also known as SLC6A3) DAT1 VNTR of the SLC6A3 gene polymorphisms), reflecting higher subcortical dopamine signaling capacity, were used to construct biologically-informed multilocus genetic profile (MGP) scores (Eisenstein et al. 2017). These elevated MGP scores were associated with reduced negative symptom severity, including anhedonia, although the associations for PA and SA did not survive multiple comparisons (Eisenstein et al. 2017). Therefore, these data suggest that striatal dopamine signaling contributes to anhedonia (Eisenstein et al. 2017). Animal studies reported the association between early life-stressors and decrease in sucrose consumption, which is considered as an indicator of anhedonia (Bolton et al. 2018). Namely, early-life

adversity provokes severe anhedonia, which is manifested as a decreased sucrose preference and reduced social play (Bolton et al. 2018). Early adversities induce anhedonia by altering interactions of pleasure/reward and stress-related networks (Bolton et al. 2018). Therefore, anhedonia appears to be induced and modulated by gene-environment interactions.

ANHEDONIA AND ANTIPSYCHOTICS

Anhedonia might be induced by dopamine D2 receptor blocking-agents such as antipsychotics (Gold et al. 2018), and, in turn, attenuated by activating dopamine D2/D3 receptors and/or by increasing dopamine sensitivity in the reward pathways (Gold et al. 2018). The relationship between antipsychotics and anhedonia is incompletely understood. All antipsychotics are highly effective in treating positive symptoms, whereas negative symptoms are difficult-to-treat (Aleman et al. 2017). However, antipsychotics might actually increase anhedonia, as the administration of D1 and D2 antagonists reduced the increase in striatal activity in response to VTA stimulation (Ferenczi et al. 2016). The effects of antipsychotics on anhedonia were investigated mostly in animal models. The effects of antipsychotics on anhedonia are not uneventful, because they depend on a type (Lemburg et al. 2011) and a dose (Berger et al. 2008) of antipsychotics. For example, quetiapine improves anhedonia in lower, whilst worsens anhedonia in higher doses (Berger et al. 2008). Aripiprazole was found to actually alleviate anhedonia in rats (Scheggi et al. 2018), and in patients with schizophrenia (Lemburg et al. 2011). It remains to be seen whether new-generation partial dopamine D2 and D3 receptor agonists, such as cariprazine and brexpiprazole, demonstrate efficacy against anhedonia. While electroconvulsive treatment was effective against anhedonia in preclinical models (Hennigsen et al. 2013), its efficacy on this domain in schizophrenia is unknown. In cross-sectional studies, the presence of anhedonia was not associated with the dose or type (typical vs. atypical) antipsychotics (Pelizza & Ferrari 2009), and SA and PA scores did not correlate with types or doses of antipsychotics (Kollias et al. 2008).

CONCLUSION

Anhedonia is increasingly being recognized as an important, but also a complex construct in schizophrenia, which might also affect a treatment response. While substantial proportion of individuals are affected by anhedonia, its relationship with nicotine dependence and lifetime suicidality remains to be investigated. Anhedonia is considered a trait-marker in schizophrenia and therefore difficult-to-treat. Given its important role in motivation and social functioning, there is an urgent need to recognize anhedonia and find an effective treatment which would target all aspects of anhedonia.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Literature search and drafting manuscript: Marina Šagud.

Critical revision of the manuscript for important intellectual content: All authors. All authors read and approved the final manuscript.

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