We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

The Many Faces of Negative Symptoms in Schizophrenia

Mihaela Fadgyas Stanculete and Octavia Capatina

Abstract

Negative symptoms are relatively frequent across schizophrenia spectrum disorders diagnostic categories and they represent deficits in different domains such as emotional, volitional and experiential. Even though negative symptoms have long been recognized as a core feature of schizophrenia, their definition has been changing over time. Different conceptualization classified this category of symptoms as primary or secondary, persistent or transient. At the current moment there are five agreed upon domains of the concept of negative symptoms, which are separated into two dimensions—experience (anhedonia, avolition, asociality) and expression (blunted affect, alogia). Multiple mechanistic pathways have been proposed and investigated for each dimension and for each domain. The current chapter attempts to address recent advances in the literature regarding the concepts, definitions and classifications of negative symptoms and their etiological model.

Keywords: anhedonia, avolition, alogia, blunted affect, negative symptoms, schizophrenia

1. Introduction

Schizophrenia is a chronic, debilitating disorder that affects approximately 1% of the world's population [1]. The disorder is a significant socioeconomic burden because of the early onset of the disease, the low remission rates, and their debilitating consequences: as the disease's progression leads to the inability, for a significant share of schizophrenic patients, to fulfill their professional, social and household roles [2]. Phenomenologically schizophrenia is considered to be a heterogeneous syndrome including several dimensions: positive, disorganization, cognitive, affective, and negative dimension. These are the most commonly reported by factor analytic studies dimensions of schizophrenia [3–5].

Negative symptoms have long been recognized as a core feature of schizophrenia, and the current studies report that their severity has a more significant impact on real-world functioning and quality of life than other categories of symptoms [6–10]. Negative symptoms, by their definition, interfere with the patient's ability to maintain social activities or personal relationships, to work or study, and even to live independently and are minimally influenced by antipsychotic medication [11–13]. Even though the attention has shifted from the positive to the negative symptoms in the last decades, the latter still represent an unmet therapeutical target, and very few pharmaceutical agents are labeling indications for negative symptoms [14–17].

Negative symptoms have been commonly described as first symptoms of schizophrenia, and very frequently, they appear during the prodromal phase of the disorder [18, 19]. The prevalence of negative symptoms is hard to establish, with reports from literature ranging between 40% and 90%, these differences result from the heterogeneity of the used definitions, constitutive factors, and assessment methods [20]. The European First Episode Schizophrenia Trial reported that at least one negative symptom was noted in up to 54.2% of the patients at baseline [21]. The Clinical Antipsychotic Trials of Interventions Effectiveness, which is one of the most extensive controlled studies for schizophrenia, reported negative symptoms in 40% of the patients [22], and the CLAMORS study reported one or more negative symptoms were present in 57.6% of patients [23]. What is known is that they can occur at any point during the illness, but the long-term course is less clear. Some studies report stability of negative domain [24], while others describe an unstable course [25]. Many factors could be accountable for this difference, but it is widely accepted that improvement in negative symptoms is more common during the first years of the disorder, and an exacerbation is frequently seen in chronic patients [26].

Across studies, it is generally evidenced that negative symptoms are frequently reported in any disease phase. They are associated with poor functional outcomes, which is why it is imperative to assess and address these symptoms to improve the quality of life for patients with schizophrenia.

2. The concept of negative symptoms in schizophrenia

2.1 Early descriptions

The classification of the symptoms of schizophrenia as being positive or negative regards the fact that positive symptoms are a surplus to normal experiences, for example, hallucinations or delusions, whereas the negative symptoms are represented by diminished experiences or expression [27]. The term of negative symptoms was borrowed from neurology, and it was coined by John Reynolds in 1858 and was introduced in psychiatry by the French psychiatrists Gaetan Gatian de Clérambault and Henry Ey [28].

The negative symptoms were considered a fundamental feature of the disease since its first descriptions by Emil Kraepelin and Eugen Bleuler [27]. Emil Kraepelin, influenced by the work of Alois Alzheimer, was the one who named the disease dementia praecox. He considered that the process underpinning the manifestation of the disease was an affective degeneration. In his treatise “Dementia praecox and paraphrenia”, he described the flat affect and the motivational deficits, which are now called negative symptoms, and he proposed the theory that the affective deficit represents the basis for the psychopathological process [27–30].

Eugen Bleuler renamed the disease schizophrenia and emphasized that there is a group of disorders under this name. At a descriptive level, he introduces a dichotomy between the symptoms of schizophrenia, and he labels the fundamental and accessory symptoms. The fundamental symptoms are described as the essence of the illness necessary to diagnose loose associations, ambivalence, affective flattening, and avolition. The accessory symptoms are hallucinations and delusions that were not necessary to diagnose schizophrenia but were highly visible and often the reason for clinical presentation. Unlike his predecessor, he considers that the affect as a process is intact in schizophrenia and that the fundamental psychopathological process is the splitting between affect and cognition, from which the symptoms of the disease arise [27, 28, 30].

The interest for negative symptoms decreased and shifted towards the positive symptoms once Chlorpromazine was developed and introduced in psychiatric wards in 1952. The awareness regarding the importance of these symptoms reemerged in the last decades because of their negative influence on the patients' real-life function [10, 11, 31].

2.2 Current perspective

The interest for the negative symptoms is constantly growing, although it has been about 40 years since Nancy Andreasen and co-workers (1982) resumed this research area and highlighted the importance of this category of symptoms. Andreasen defined twenty negative symptoms, which were grouped into five factors: flat affect, alogia, avolition/apathy, anhedonia/social withdrawal, and attention deficit. She proposed that negative and positive symptoms are part of a continuum representing the extreme and opposite poles of this continuum. Patients presenting mixed symptoms, positive and negative symptoms, were considered intermediate patients [28, 32].

Later, Timothy Crow [33] postulated the hypothesis of two types of disease, schizophrenia type I and type II. Type I is characterized by positive symptoms (hallucinations, delusions), showing a good response to neuroleptic medication, without intellectual deficit, and with an increase in D2 receptors. Type II is characterized by negative symptoms (alogia, affective flattening, decreased interest, and pleasure), an inadequate response to neuroleptic medication, intellectual deficits, and changes in the temporal lobes' neural structures. According to this author, type I could develop negative symptoms and progress to type II, but type II could not transform into type I, even though positive symptoms could appear [33].

In 1988 William Carpenter and collaborators brought to attention a new perspective on the concept of negative symptoms and made an essential distinction between idiopathic, primary negative symptoms and secondary negative symptoms. Secondary negative symptoms occur as side effects of neuroleptic medication (extrapyramidal symptoms, sedation) or secondary to depression, social deprivation or substimulation or secondary to positive symptoms (active social withdrawal secondary to paranoid ideation, or diminished expression, which could be a coping strategy for patients in an acute psychotic episode who are unable to process tumultuous hallucinations). At a phenomenological level, primary and secondary negative are very similar and yet very hard to distinguish. The diagnosis of primary negative symptoms, according to Carpenter, should be only a diagnosis of exclusion. The importance of distinguishing these categories of symptoms is that secondary negative symptoms may be responsive to specific treatments [34].

As a result of this classification, deficit schizophrenia was introduced to define patients with primary and persistent negative symptoms. The dichotomy, deficit/non-deficit schizophrenia, is based exclusively on the presence or absence of primary and stable negative symptoms [34]. The diagnostic criteria for deficit schizophrenia are presented in **Table 1**. Several subsequent studies have compared patients with deficit schizophrenia versus non-deficit schizophrenia and found overwhelming evidence that the two types are different in that concerns risk factors, premorbid functioning, disease evolution, neurobiological basis, and response to treatment. The clinical picture of deficit schizophrenia shows more significant social withdrawal, anergia, more severe cognitive impairments, poorer premorbid adjustment than non-deficit schizophrenia, and often summer birth instead of non-deficit schizophrenia, which predominates winter birth [37–41]. Although the two diagnostic categories have been validated in several studies, the evolution over time of negative symptoms does not always allow a clear distinction between

a. The presence of at least two of the following six negative symptoms: <ul style="list-style-type: none">i. Decreased emotional expression (observed behavior);ii. Affective flattening (e.g. a narrow range of the patient's subjective emotional experience);iii. Alogia;iv. Diminished interests;v. Diminished goals;vi. Diminished social interest;
b. The presence of symptoms described in point (a) for at least 12 months including periods of clinical stability;
c. The symptoms described at point (a) are primary symptoms, not secondary to other factors such as anxiety, medication side effects, psychotic symptoms, intellectual disability or depression;
d. The patient meets the DSM criteria (3rd edition, or later editions) for schizophrenia.

Table 1.
Diagnostic criteria for deficit schizophrenia [34–36].

primary and secondary symptoms, making the diagnosis very difficult. Moreover, first psychotic episode patients represent another diagnostical challenge [42–44].

A different approach, which tried to reduce the heterogeneity of negative symptoms, was proposed by the National Institute for Mental Health (USA) in The Consensus Statement on Negative Symptoms (2006), which defined the constitutive factors of the negative domain: flat affect, alogia, social withdrawal, avolition, and anhedonia, essentially the same areas that have been defined by Nancy Andreasen (1982) except for the attention deficit. A short definition of each symptom, according to this consensus, is presented in **Table 2** [45].

As a result of the same consensus, the National Institute for mental Health defined the concept of persistent negative symptoms, which is more applicable in the clinical setting than the concept of deficit schizophrenia because of its more permissive criteria. The criteria for the persistent negative symptoms imply only a period of six months, with at least moderate intensity negative symptoms and low levels of positive, depressive, and extrapyramidal symptoms. Secondary negative symptoms can be included in this category if they are not responsive to a specific treatment [45].

In the attempt to describe the nature, the etiology, and find operational criteria for research in the field, other specific terms were defined: predominant, prominent, enduring/non-enduring negative symptoms. Unfortunately, there is

Flat affect	A decrease in the expression of emotions and emotional reactivity to events, observed spontaneously during speech or after targeted questions (facial expression, intonation, and gestures)
Alogia	Quantitative reduction of speech and spontaneity (the amount of information spontaneously developed by the patient in addition to the necessary answers to the questions).
Social withdrawal	Interactions and initiatives to have social contacts are diminished due to decreased motivation and decreased desire to form or maintain relationships with other people.
Anhedonia	Diminished experience of pleasure for a variety of activities or events, over time of the activities or events (consumer anhedonia) or for subsequent activities and events (anticipatory anhedonia)
Avolition	Reducing the initiative and persistence of goal-oriented activities due to diminished motivation

Table 2.
Definition of negative symptoms of schizophrenia [45].

no consensus regarding the exact definition of any of these terms as they were only used for research purposes [9].

Up to the present point, negative symptoms are considered to represent a heterogeneous domain of psychopathology. Recent factor analytic studies have provided evidence that the domain of negative symptoms can be grouped into two factors: avolition/apathy and diminished expression. The apathy/avolition subdomain includes avolition, social withdrawal, and anhedonia, and the diminished expression includes affective flattening and alogia [46–48]. This factorial structure has been confirmed by several studies using different scales for the evaluation of negative symptoms: Scale for the Assessment of Negative Symptoms (SANS), Positive and Negative Syndrome Scale (PANSS), Negative Symptoms Assessment Scale (NSA-16) and more recently developed scales Clinical Assessment Interview for Negative Symptoms (CAINS) and Brief Negative Symptom Scale (BNSS), which were specially developed to evaluate this factorial structure [49, 50]. Several studies have compared the importance of these domains regarding clinical features, disease progression, and impact on functioning. The domain of diminished expression (DE) turned out to be more persistent over time, have a higher prevalence in the early stages of the disease, and be associated with a longer duration of the prodromal phase of the disease than the apathy/avolition (AA) [51–53]. The AA domain is associated with poorer functioning, with a longer duration of untreated psychosis and non-adherence to treatment. These associations were not reported for the DE domain [47, 52, 54]. Research up to this point provided evidence that the AA and DE domains represent different clinical aspects of schizophrenia. Moreover, if these areas have different etiologies and should be approached differently from a therapeutic point of view are elements in an ongoing investigation, neuroimaging studies currently support this hypothesis [8, 55].

To date, no consensus has been reached on how to approach negative symptoms: categorical versus dimensional. Numerous studies demonstrated the validity of deficit schizophrenia construct or the subtype characterized by primary and persistent negative symptoms [51, 52, 54]. However, the dimensional approach is supported by several studies that have shown the presence of negative symptoms in other disorders than schizophrenia, such as schizoaffective disorder, depression, Parkinson's disease, Huntington's disease, Alzheimer's disease, temporal lobe epilepsy, and even in the general population [8, 55, 56].

3. The neurobiology of negative symptoms in schizophrenia

The heterogeneity in etiology and clinical manifestation of the negative symptoms in schizophrenia led to the exploration of several structural abnormalities, pathways, and mechanisms which may underlie this complex of symptoms. The attempt to reduce these symptoms' heterogeneity leads to concepts of deficit and non-deficit schizophrenia and diminished expression and avolition/apathy domains. Different hypotheses have been constructed for these models' pathophysiological mechanisms, but unfortunately without fully satisfying results [8, 9, 55, 56].

3.1 Deficit schizophrenia versus non-deficit schizophrenia

After deficit schizophrenia was described, several studies brought out data supporting the hypothesis that deficit schizophrenia differs from non-deficit schizophrenia in terms of risk factors, premorbid functioning, the evolution of the disease, neurobiological basis, and response to treatment [37–41]. Epidemiological

studies support a prevalence of deficit schizophrenia: 15% of patients with a first episode of the disease, 25–30% in clinical trials, and 14–17% in population studies [37, 57, 58]. Structural and functional brain imaging studies have highlighted several differences between patients with deficit and non-deficit schizophrenia. Abnormalities and asymmetries in the temporal lobe level, cerebrospinal fluid accumulations in the left temporal lobe, volume reduction of the right temporal lobe have been reported in patients with deficit schizophrenia compared with patients with non-deficit schizophrenia and healthy subjects. Both groups of patients had a reduced volume of the dorsolateral prefrontal cortex and temporal lobes than healthy subjects [59, 60]. Several studies have reported white matter abnormalities, especially in the frontoparietal and frontotemporal circuits in patients with deficit schizophrenia. These patients present discontinuities in the inferior longitudinal fasciculus, arcuate fasciculus, and uncinate fasciculus, and it has been suggested that there may be a connection between these structural changes and the social and emotional dysfunctions characteristic for deficit schizophrenia [59, 60]. Functional imaging investigations report a decrease in glucose metabolism and a decrease in the frontal and parietal lobes' blood flow in cases of deficit schizophrenia versus non-deficit schizophrenia or healthy volunteers [61, 62]. Studies that used functional MRI to assess the response to the reward reported a reduction of dorsal caudate nucleus activity in patients with deficit schizophrenia [63, 64].

Regarding the treatment of deficit schizophrenia, respectively of primary negative symptoms, the efficacy of several antipsychotics was evaluated: clozapine, olanzapine, zotepine, and amisulpride. These therapeutic options are superior to placebo therapy and first-generation antipsychotics, but not other classes of atypical antipsychotics, data suggesting that they would be effective for secondary negative symptoms [65–68]. Recent studies have evaluated the efficacy of add-on therapies with agents that stimulate NMDA receptors: glycine, D-serine, and D-cycloserine, but no significant improvement in symptoms was reported on the primary negative ones [15, 40, 69, 70].

3.2 Persistent negative symptoms

Persistent negative symptoms are a looser category than deficit schizophrenia as potential causes of secondary negative symptoms are not completely ruled out, but it is assumed that the secondary negative symptoms' clinical expression is mild [45]. Also, this category includes all negative symptoms, primary or secondary, that do not respond to commonly used treatments, which are apparent during periods of clinical stability of the disease and interfere with the patient's functionality [45]. There is great variability in the prevalence of persistent negative symptoms due to different definitions used for this category. Prevalence of persistent negative symptoms are higher than deficit schizophrenia and were estimated between 35% and 60% [21, 71–73].

Structural and functional imaging studies have reported volume reduction of the gray matter in the temporal lobes, cortical atrophy of the right superior temporal gyrus, right parahippocampal gyrus, and left orbitofrontal gyrus, and that structural abnormality of the white matter in the frontal lobes could be associated with persistent negative symptoms [74–77].

Dopaminergic antagonism is the only common mechanism of drugs used to treat psychosis. However, subcortical dopamine excess is accompanied by a prefrontal dopaminergic function, which encompasses a reduced D1 receptor activation in the prefrontal cortex, dopamine hypoactivity in the caudate nucleus, and modifications

in D3 receptor activity. These alterations appear to contribute to the pathogenesis of negative symptoms. Cariprazine is an atypical antipsychotic that is a partial agonist of dopamine receptors D3 and D2, with high selectivity for D3 receptors, which have been shown to be effective for predominant negative symptoms [78, 79]. Another compound, MIN-101, that has no affinity for dopaminergic receptors and acts on sigma-2 and serotonergic receptors 5-HT_{2A} effectively reduces persistent negative symptoms [80].

3.3 Negative symptoms domains: avolition/apathy and diminished expression

Factor analysis studies have suggested that negative symptoms include two domains: apathy/avolition and diminished expression, which led to building separate hypotheses for these domains [45, 47, 52]. In current conceptualizations, the avolition/apathy domain is defined as deficits in different motivation areas. Two possible mechanisms and circuits are considered to be involved: the reward circuit and the salience circuit [81]. Functional MRI studies tried to elucidate the substrate of the motivational deficit using tasks involving reward anticipation, and it was found that there is an association between the activation of the ventral striatum and the apathy/avolition domain. This relationship has not been confirmed for the diminished expression domain. Only a limited number of studies have investigated the correlations between neural structures and the apathy/avolition domain, and the following results were reported: a low volume of the frontal lobes, thinning of the anterior cingulate cortex and orbitofrontal cortex, and structural abnormalities of connectivity between the medial orbitofrontal cortex and the anterior rostral cingulate cortex [55, 82–85].

Cognitive-behavioral therapy was the first form of alternative therapy targeting poor motivation, anhedonia, and irrational cognitions. It promotes the patient's involvement in defining goals and aims and targets, improving functionality and recovery of the patients. A positive effect of cognitive-behavioral therapy on negative symptoms in combination with antipsychotic medication has been proved, and the beneficial effects persist even after stopping therapy. Functional changes, highlighted by functional brain imaging studies, at striatal levels underlie this type of therapy's effectiveness [86, 87].

Some studies suggest that dopaminergic agonists: methylphenidate, amphetamine, lisdexamfetamine, modafinil, selegiline are involved in relieving negative symptoms without worsening the positive symptoms. The exact mechanisms by which this class acts are not completely elucidated. Increasing dopamine and nor-adrenaline at the frontocortical level or the dopamine action at the striatal limbic level are possible mechanisms involved in the assumed action of dopaminergic agonists on a motivational deficit [17, 55, 88].

The inflammatory hypothesis of schizophrenia suggests that alterations in the prenatal immune system are involved in the disease's etiology. Anti-inflammatory agents studied so far are pregnenolone, acetylsalicylic acid, cyclooxygenase-2, minocycline, N-acetylcysteine, and omega-3 fatty acids. To date, clinical trials have seemed promising, but these studies need to be replicated on a larger scale [89–92].

High frequency transcranial magnetic stimulation (≤ 10 Hz) intensifies metabolism and excitability in the prefrontal cortex. It has been proved to be effective in treating negative symptoms when applied in the early stages of schizophrenia. The mechanisms of action of this method involve modulation of NMDA receptors and striatal dopamine release. This technique has not been proven effective for alogia, but only for the other negative symptoms [93, 94].

Transcranial direct current stimulation has been mainly studied for positive symptoms, auditory hallucinations, but an improvement of negative symptoms as a subsidiary result, especially motivational deficits, has been reported. The modulation of cortical–subcortical networks can explain the benefits for negative symptoms [95, 96].

The diminished expression domain's pathophysiological mechanisms have received less attention than those involved in the apathy/avolition domain. It has been hypothesized that this domain is correlated with neurocognitive deficits and social cognition deficits [97]. In treatment naïve patients, there is an association between expressive deficits and neurological soft signs, which suggests the existence of diffuse neurodevelopmental abnormalities. Functional neuroimaging studies that investigated impaired emotional processing have shown a hypoactivity of different neural networks: the prefrontal, ventrolateral cortex, the amygdala, cingulate cortex, and the cuneus [98–100]. Activation of the anterior rostral cingulate cortex was negatively correlated with the diminished expression domain in the tasks which involve an interaction between reward and cognition [101].

Cognitive training, which aims to improve neurocognitive skills and social cognition, has been shown to restore the disrupted neural networks in the prefrontal cortex and anterior rostral cingulate cortex [102].

Social skills training for emotion perception, recognition, and expression, aims to educate patients about the necessity of social skills, verbal and nonverbal communication improvement, and it has been shown that it facilitates the release of oxytocin [103]. Considering the hypothesis that the strengthening social cognition could have beneficial effects on the diminished expression, the administration of intranasal oxytocin was studied, given its action on serotonin and dopamine in the nucleus accumbens and amygdala. Oxytocin is effective in emotion recognition and the theory of mind as add-on therapy and being used in the long term [104].

4. Genetic basis of negative symptoms

The progress in the genetics of schizophrenia in the last years has been noticeable. Heritability represents a statistical estimate to quantitate the relative genetic contribution to a trait relative to its environmental contributors. Heritability is the amount or proportion of phenotypic variance of the disease of interest in the population that is inherited through genetic factors. The heritability of schizophrenia has been established at 81% [105], making the genetic factor the most significant for the disease.

According to evidence from previous family and association studies, it has been suggested that genetic factors are involved in the development of schizophrenia and also in its clinical presentation. Studies that investigated genes potentially involved in negative symptoms pathogenesis highlighted that classifying patients with schizophrenia into specific subtypes based on predominant symptoms is useful for selecting the specific treatment. The findings, and references for these studies are summarized on **Table 3**.

Genetics is rapidly growing, with technological discoveries making it increasingly possible to identify common and rare variants on genomic DNA. Much new and confirmatory work remains to be performed to elucidate the role of specific genetic variants in negative symptoms development and the distinct ways the genes and environment interact to result in schizophrenia susceptibility.

Author	Year	Findings	Journal
Fanous et al.	2005	Variation in DTNBP1 may predispose subjects to a form of schizophrenia with high levels of negative symptoms.	American Journal of Psychiatry [106]
DeRosse et al.	2006	Significant association between the CTCTAC haplotype and lifetime severity of negative symptoms in patients with schizophrenia.	American Journal of Psychiatry [107]
Pelayo-Terán et al.	2008	Patients with a Val158 homozygote genotype had a higher severity of negative symptoms at the onset of the schizophrenia	American Journal of Medical Genetics [108]
Wessman et al.	2009	DTNBP1 gene is associated with a schizophrenia phenotype characterized by prominent negative symptoms	Biological Psychiatry [109]
Bertolino et al.	2009	Negative symptoms were weakly associated with promoter rs1236428	Brain [110]
Petrovsky et al.	2010	Association of prepulse inhibition deficits and polymorphisms in the α3 subunits of the CHRNA gene cluster. CHRNA3 polymorphisms were also associated with negative symptoms	Neuropsychopharmacology [111]
Xu et al.	2013	Common genetic variations (ST3GAL1, RNF144, CTNNA3 and ZNF385D) are associated with negative symptoms of schizophrenia using meta-analysis.	PloS one [112]
Mezquida et al.	2016	BDNF Val66Met polymorphism is associated with negative symptoms severity	European Psychiatry [113]
Edwards et al.	2016	NKAIN2 was significantly associated with negative symptoms	Schizophrenia bulletin [114]
Gao et al.	2018	Abnormal peripheral gene expression DNA methylation of MMP9 possible biomarker for negative symptom	Frontiers in Genetics [115]
Schneider et al.	2019	Negative symptoms are core manifestations of psychosis in individuals with 22q11DS that strongly impact global functioning.	Schizophrenia Research [116]
Abbreviations: DTNBP1 (dystrobrevin binding protein 1), CHRNA3 (nicotinic acetylcholine receptor), BDNF (brain-derived neurotrophic factor), MMP9 (Matrix metalloproteinase-9), NKAIN2 (Sodium/Potassium Transporting ATPase Interacting 2), 22q11DS (22q11 deletion syndrome).			

Table 3.
Genes potentially involved in negative symptoms' pathogenesis.

5. Conclusions

Conceptual work has highlighted that negative symptoms can be defined as primary or secondary, persistent, or transient, and they encompass two distinct domains: avolition/apathy and diminished expression. Deficit schizophrenia is defined as primary enduring negative symptoms, but more operative for research and clinical setting is the concept of persistent negative symptoms. Considering the heterogeneity of negative symptoms has brought some progress in research on their genetic and neurobiological basis and treatment approaches. Unfortunately, their underlying pathophysiology is still unknown, and the treatment remains a critical unmet need.

Several hypotheses have been proposed for the pathophysiology of schizophrenia, from which the dopaminergic hypothesis remains the leading one. The

dopaminergic hypofunction of the frontal lobe and the mesolimbic structures seems to be underlying the negative symptoms. Despite the advances in the field, many clinical trials still consider the negative symptoms as a monolithic construct which might be the reason for the unsatisfactory results.

Further research directions should concentrate on the two distinct negative symptoms dimensions apathy/avolition and diminished expression, and even further on each symptom and its pathophysiology. Another interesting approach is the transdiagnostic one, which could be helpful in the attempt to disentangle the mechanisms underlying this category of symptoms by using information gathered from depression or Parkinson's disease.

Conflict of interest

The authors declare no conflict of interest.

Author details

Mihaela Fadgyas Stanculete* and Octavia Capatina
Department of Neurosciences, University of Medicine and Pharmacy Iuliu
Hatieganu, Cluj Napoca, Romania

*Address all correspondence to: mihaelastanculete@yahoo.com

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Kahn R, Sommer I, Murray R, Meyer-Lindenberg A, Weinberger D, Cannon T et al. Schizophrenia. *Nature Reviews Disease Primers*. 2015;1(1).
- [2] Charlson F, Ferrari A, Santomauro D, Diminic S, Stockings E, Scott J et al. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophrenia Bulletin*. 2018;44(6):1195-1203.
- [3] Lindenmayer, J. P., Grochowski, S., & Hyman, R. B. (1995). Five factor model of schizophrenia: replication across samples. *Schizophrenia research*, 14(3), 229-234.
- [4] Wallwork, R. S., Fortgang, R., Hashimoto, R., Weinberger, D. R., & Dickinson, D. (2012). Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. *Schizophrenia research*, 137(1-3), 246-250.
- [5] van der Gaag, M., Cuijpers, A., Hoffman, T., Remijnsen, M., Hijman, R., de Haan, L., ... & Wiersma, D. (2006). The five-factor model of the Positive and Negative Syndrome Scale I: confirmatory factor analysis fails to confirm 25 published five-factor solutions. *Schizophrenia research*, 85(1-3), 273-279.
- [6] Fervaha, G., Foussias, G., Agid, O., & Remington, G. (2014). Impact of primary negative symptoms on functional outcomes in schizophrenia. *European Psychiatry*, 29(7), 449-455.
- [7] Jonathan Rabinowitz, Stephen Z. Levine, George Garibaldi, Dragana Bugarski-Kirola, Carmen Galani Berardo, Shitij Kapur, Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: Analysis of CATIE data, *Schizophrenia Research*, Volume 137, Issues 1-3,
- [8] Foussias, G., Agid, O., Fervaha, G., & Remington, G. (2014). Negative symptoms of schizophrenia: clinical features, relevance to real world functioning and specificity versus other CNS disorders. *European Neuropsychopharmacology*, 24(5), 693-709.
- [9] Correll CU, Schooler NR. Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. *Neuropsychiatr Dis Treat*. 2020 Feb 21;16:519-534. doi: 10.2147/NDT.S225643. PMID: 32110026; PMCID: PMC7041437.
- [10] Harvey PD, Strassnig M. Predicting the severity of everyday functional disability in people with schizophrenia: cognitive deficits, functional capacity, symptoms, and health status. *World Psychiatry*. 2012;11(2):73-79. doi:10.1016/j.wpsyc.2012.05.004
- [11] Foussias, G., Mann, S., Zakzanis, K. K., Van Reekum, R., Agid, O., & Remington, G. (2011). Prediction of longitudinal functional outcomes in schizophrenia: the impact of baseline motivational deficits. *Schizophrenia research*, 132(1), 24-27.
- [12] CĂPĂȚÎNĂ, O., & MICLUȚIA, I. (2018). Internalized stigma as a predictor of quality of life in schizophrenia. *Journal of Evidence-Based Psychotherapies*, 18(2), 35-53.
- [13] Sicras-Mainar, A., Maurino, J., Ruiz-Beato, E., & Navarro-Artieda, R. (2014). Impact of negative symptoms on healthcare resource utilization and associated costs in adult outpatients with schizophrenia: a population-based study. *BMC psychiatry*, 14(1), 1-8.
- [14] Möller HJ. The Relevance of Negative Symptoms in Schizophrenia and How to Treat Them with

- Psychopharmaceuticals? Psychiatr Danub. 2016 Dec;28(4):435-440. PMID: 27855437.
- [15] Fusar-Poli, P., Papanastasiou, E., Stahl, D., Rocchetti, M., Carpenter, W., Shergill, S., & McGuire, P. (2015). Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. *Schizophrenia bulletin*, 41(4), 892-899.
- [16] Aleman A, Lincoln TM, Bruggeman R, Melle I, Arends J, Arango C, Knegtering H. Treatment of negative symptoms: Where do we stand, and where do we go? *Schizophr Res*. 2017 Aug;186:55-62. doi: 10.1016/j.schres.2016.05.015. Epub 2016 Jun 9. PMID: 27293137.
- [17] Căpățînă, O.O., Micluția, I.V., & Fadgyas-Stănculete, M. (2021). Current perspectives in treating negative symptoms of schizophrenia: A narrative review (Review). *Experimental and Therapeutic Medicine*, 21, 276. <https://doi.org/10.3892/etm.2021.9707>
- [18] Piskulic D, Addington J, Cadenhead KS, et al. Negative symptoms in individuals at clinical high risk of psychosis. *Psychiatry Res*. 2012;196(2-3):220-224. doi:10.1016/j.psychres.2012.02.018
- [19] Velthorst E, Nieman DH, Becker HE, et al. Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. *Schizophr Res*. 2009;109(1-3):60-65. doi:10.1016/j.schres.2009.02.002
- [20] Mäkinen J, Miettunen J, Isohanni M, Koponen H. Negative symptoms in schizophrenia: a review. *Nord J Psychiatry*. 2008;62 (5):334-341. doi:10.1080/08039480801959307
- [21] Galderisi, S., Mucci, A., Bitter, I., Libiger, J., Bucci, P., Fleischhacker, W. W., ... & Eufest Study Group. (2013). Persistent negative symptoms in first episode patients with schizophrenia: results from the European First Episode Schizophrenia Trial. *European Neuropsychopharmacology*, 23(3), 196-204.
- [22] Rabinowitz, J., Berardo, C. G., Bugarski-Kirola, D., & Marder, S. (2013). Association of prominent positive and prominent negative symptoms and functional health, well-being, healthcare-related quality of life and family burden: a CATIE analysis. *Schizophrenia research*, 150(2-3), 339-342.
- [23] Bobes, J., Arango, C., Garcia-Garcia, M., & Rejas, J. (2009). Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: findings from the CLAMORS study. *The Journal of clinical psychiatry*, 71(3), 280-286.
- [24] Austin SF, Mors O, Budtz-Jorgensen E, et al. Long-term trajectories of positive and negative symptoms in first episode psychosis: a 10year follow-up study in the OPUS cohort. *Schizophr Res*. 2015;168(1-2):84-91. doi:10.1016/j.schres.2015.07.021
- [25] Heilbronner U, Samara M, Leucht S, Falkai P, Schulze TG. The Longitudinal Course of Schizophrenia Across the Lifespan: Clinical, Cognitive, and Neurobiological Aspects. *Harv Rev Psychiatry*. 2016 Mar-Apr;24(2):118-28. doi: 10.1097/HRP.0000000000000092. PMID: 26954596; PMCID: PMC5079232.
- [26] Pogue-Geile MF, Harrow M. Negative symptoms in schizophrenia: their longitudinal course and prognostic importance. *Schizophr Bull*. 1985;11(3):427-439. doi:10.1093/schbul/11.3.427
- [27] Marneros A, Andreasen N, Tsuang M. Negative versus positive

schizophrenia. Berlin: Springer-Verlag; 1991.

Archives of General Psychiatry. 2001;58(2):165.

[28] Malaspina D, Walsh-Messinger J, Gaebel W, Smith L, Gorun A, Prudent V et al. Negative symptoms, past and present: A historical perspective and moving to DSM-5. *European Neuropsychopharmacology*. 2014;24(5):710-724.

[38] Blanchard J, Horan W, Collins L. Examining the latent structure of negative symptoms: Is there a distinct subtype of negative symptom schizophrenia?. *Schizophrenia Research*. 2005;77(2-3):151-165.

[29] Kraepelin E. *Dementia praecox and paraphrenia*. Miami, FL: HardPress Pub.; 2013.

[39] Messias E, Kirkpatrick B, Bromet E, Ross D, Buchanan B, Carpenter W et al. Summer birth and deficit schizophrenia: A pooled analysis from five countries. *Schizophrenia Research*. 2003; 60(1):45-46.

[30] Andreasen N. The evolving concept of schizophrenia: From Kraepelin to the present and future. *Schizophrenia Research*. 1997;28(2-3):105-109.

[40] Galderisi S, Maj M. Deficit schizophrenia: An overview of clinical, biological and treatment aspects. *European Psychiatry*. 2009;24(8): 493-500.

[31] Ban TA. Fifty years chlorpromazine: a historical perspective. *Neuropsychiatric Disease and Treatment*. 2007;3(4):495-500.

[41] Galderisi S, Quarantelli M, Volpe U, Mucci A, Cassano G, Invernizzi G et al. Patterns of Structural MRI Abnormalities in Deficit and Nondeficit Schizophrenia. *Schizophrenia Bulletin*. 2007;34(2):393-401.

[32] Andreasen N. Negative v Positive Schizophrenia. *Archives of General Psychiatry*. 1982;39(7):789

[42] Buchanan R. Persistent Negative Symptoms in Schizophrenia: An Overview. *Schizophrenia Bulletin*. 2007;33(4):1013-1022.

[33] Crow - Crow T. The Two-syndrome Concept: Origins and Current Status. *Schizophrenia Bulletin*. 1985;11(3): 471-488.

[43] Mäkinen J, Miettunen J, Isohanni M, Koponen H. Negative symptoms in schizophrenia—A review. *Nordic Journal of Psychiatry*. 2008;62(5): 334-341.

[34] Carpenter W, Heinrichs D, Wagman A. Deficit and nondeficit forms of schizophrenia: the concept. *American Journal of Psychiatry*. 1988;145(5):578-583.

[35] Diagnostic and statistical manual of mental disorders. DSM-III-R. Prep. Washington: American Psychiatric Ass; 1987.

[44] Kelley M, Haas G, van Kammen D. Longitudinal progression of negative symptoms in schizophrenia: A new look at an old problem. *Schizophrenia Research*. 2008;105(1- 3):188-196.

[36] Diagnostic and statistical manual of mental disorders. DSM-IV. Washington, DC: American Psychiatric Association; 1995.

[45] Kirkpatrick B, Fenton W, Carpenter W, Marder S. The NIMH-MATRICES Consensus Statement on Negative Symptoms. *Schizophrenia Bulletin*. 2006;32(2):214-219.

[37] Kirkpatrick B, Buchanan R, Ross D, Carpenter W. A Separate Disease Within the Syndrome of Schizophrenia.

- [46] Blanchard J, Cohen A. The Structure of Negative Symptoms Within Schizophrenia: Implications for Assessment. *Schizophrenia Bulletin*. 2005;32(2):238-245.
- [47] Messinger J, Trémeau F, Antonius D, Mendelsohn E, Prudent V, Stanford A et al. Avolition and expressive deficits capture negative symptom phenomenology: Implications for DSM-5 and schizophrenia research. *Clinical Psychology Review*. 2011;31(1):161-168.
- [48] Park S, Llerena K, McCarthy J, Couture S, Bennett M, Blanchard J. Screening for negative symptoms: Preliminary results from the self-report version of the Clinical Assessment Interview for Negative Symptoms. *Schizophrenia Research*. 2012;135(1-3):139-143.
- [49] Kirkpatrick B, Strauss G, Nguyen L, Fischer B, Daniel D, Cienfuegos A et al. The Brief Negative Symptom Scale: Psychometric Properties. *Schizophrenia Bulletin*. 2010;37(2):300-305. 48. Mucci A, Galderisi S. The second-generation assessment scales: Brief negative symptom scale and clinical assessment interview for negative symptoms. *European Psychiatry*. 2016;33:S70.
- [50] Horan W, Kring A, Gur R, Reise S, Blanchard J. Development and psychometric validation of the Clinical Assessment Interview for Negative Symptoms (CAINS). *Schizophrenia Research*. 2011;132(2-3):140-145.
- [51] Galderisi S, Bucci P, Mucci A, Kirkpatrick B, Pini S, Rossi A, Vita A, Maj M. Categorical and dimensional approaches to negative symptoms of schizophrenia: focus on long-term stability and functional outcome. *Schizophr Res*. 2013 Jun;147(1):157-62.
- [52] Strauss GP, Horan WP, Kirkpatrick B, Fischer BA, Keller WR, Miski P, Buchanan RW, Green MF, Carpenter WT Jr. Deconstructing negative symptoms of schizophrenia: avolition-apathy and diminished expression clusters predict clinical presentation and functional outcome. *J Psychiatr Res*. 2013 Jun;47(6):783-90.
- [53] Liemburg E, Castelein S, Stewart R, van der Gaag M, Aleman A, Knegtering H; Genetic Risk and Outcome of Psychosis (GROUP) Investigators, 2013. Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. *J. Psychiatr. Res.* 47, 178-725. <http://dx.doi.org/10.1016/j.jpsychires.2013.01.024>
- [54] Rocca P, Montemagni C, Zappia S, Piterà R, Sigaudò M, Bogetto F. Negative symptoms and everyday functioning in schizophrenia: A cross-sectional study in a real world-setting. *Psychiatry Research*. 2014;218(3):284-289.
- [55] Galderisi S, Mucci A, Buchanan R, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. *The Lancet Psychiatry*. 2018;5(8):664-677.
- [56] Marder S, Galderisi S. The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry*. 2017;16(1):14-24.
- [57] Kirkpatrick B, Castle D, Murray, R.M., Carpenter Jr WT. Risk factors for the deficit syndrome of schizophrenia. *Schizophr. Bull*. 2000: 26 (1), 233-242.
- [58] Kirkpatrick B. The deficit syndrome: Marker of a separate disease within schizophrenia. *Biological Psychiatry*. 1997;42(1):203S.
- [59] Turetsky BI, Colbath EA, Gur RE. P300 subcomponent abnormalities in schizophrenia: I. Physiological evidence for gender and subtype specific differences in regional pathology. *Biol. Psychiatry*. 1998; 43 (2), 84-96.

- [60] Galderisi S, Quarantelli M, Volpe U, Mucci A, Cassano GB, Invernizzi G, Rossi A, Vita A, Pini S, Cassano P, Daneluzzo E, De Peri L, Stratta P, Brunetti A, Maj M. Patterns of structural MRI abnormalities in deficit and nondeficit schizophrenia. *Schizophr. Bull.* 2008;34 (2), 393-401.
- [61] Gonul A, Kula M, Eşel E, Tutuş A, Sofuoğlu S. A Tc-99m HMPAO SPECT study of regional cerebral blood flow in drug-free schizophrenic patients with deficit and non-deficit syndrome. *Psychiatry Research: Neuroimaging.* 2003;123(3):199-205.
- [62] Tamminga C. Limbic System Abnormalities Identified in Schizophrenia Using Positron Emission Tomography With Fluorodeoxyglucose and Neocortical Alterations With Deficit Syndrome. *Archives of General Psychiatry.* 1992;49(7):522-530.
- [63] Mucci A, Dima D, Soricelli A, Volpe U, Bucci P, Frangou S et al. Is avolition in schizophrenia associated with a deficit of dorsal caudate activity? A functional magnetic resonance imaging study during reward anticipation and feedback. *Psychological Medicine.* 2015;45(08):1765-1778.
- [64] Morris R, Quail S, Griffiths K, Green M, Balleine B. Corticostriatal Control of Goal-Directed Action Is Impaired in Schizophrenia. *Biological Psychiatry.* 2015;77(2):187-195.
- [65] Lindenmayer J, Khan A, Iskander A, Abad M, Parker B. A Randomized Controlled Trial of Olanzapine Versus Haloperidol in the Treatment of Primary Negative Symptoms and Neurocognitive Deficits in Schizophrenia. *The Journal of Clinical Psychiatry.* 2007;68(03):368-379.
- [66] Murphy B, Chung Y, Park T, McGorry P. Pharmacological treatment of primary negative symptoms in schizophrenia: A systematic review. *Schizophrenia Research.* 2006;88(1- 3):5-25.
- [67] Leucht S. Amisulpride, an Unusual "Atypical" Antipsychotic: A Meta-Analysis of Randomized Controlled Trials. *American Journal of Psychiatry.* 2002;159(2):180-190.
- [68] Möller H, Riedel M, Müller N, Fischer W, Kohnen R. Zotepine Versus Placebo in the Treatment of Schizophrenic Patients with Stable Primary Negative Symptoms: A Randomized Double-Blind Multicenter Trial. *Pharmacopsychiatry.* 2004;37(6):270-278.
- [69] Maj M, Galderisi S. Deficit schizophrenia: a valid categorical subtype of schizophrenia?. *Schizophrenia Research.* 2008;102(1-3):45.
- [70] Arango C, Garibaldi G, Marder S. Pharmacological approaches to treating negative symptoms: A review of clinical trials. *Schizophrenia Research.* 2013;150(2-3):346-352.
- [71] Üçok A, Ergül C. Persistent negative symptoms after first episode schizophrenia: A 2-year follow-up study. *Schizophrenia Research.* 2014;158(1-3):241-246.
- [72] López-Díaz Á, Lara I, Lahera G. Is the Prevalence of the Deficit Syndrome in Schizophrenia Higher than Estimated? Results of a Meta-Analysis. *Psychiatry Investigation.* 2018;15(1):94-98.
- [73] Bobes J, Arango C, Garcia-Garcia M, Rejas J. Prevalence of Negative Symptoms in Outpatients With Schizophrenia Spectrum Disorders Treated With Antipsychotics in Routine Clinical Practice. *The Journal of Clinical Psychiatry.* 2009;71(03):280-286.
- [74] Meisenzahl E, Koutsouleris N, Bottlender R, Scheuerecker J, Jäger M,

- Teipel S et al. Structural brain alterations at different stages of schizophrenia: A voxel-based morphometric study. *Schizophrenia Research*. 2008;104(1-3):44-60.
- [75] Sigmundsson T, Suckling J, Maier M, Williams S, Bullmore E, Greenwood K et al. Structural Abnormalities in Frontal, Temporal, and Limbic Regions and Interconnecting White Matter Tracts in Schizophrenic Patients With Prominent Negative Symptoms. *American Journal of Psychiatry*. 2001;158(2):234-243.
- [76] Bodnar M, Hovington C, Buchy L, Malla A, Joober R, Lepage M. Cortical Thinning in Temporo-Parietal Junction (TPJ) in Non-Affective First-Episode of Psychosis Patients with Persistent Negative Symptoms. *PLoS ONE*. 2014;9(6):e101372.
- [77] Hovington C, Lepage M. Neurocognition and neuroimaging of persistent negative symptoms of schizophrenia. *Expert Review of Neurotherapeutics*. 2012;12(1):53-69.
- [78] Orsolini L, Valchera A, De Berardis D, Vecchiotti R, Iasevoli F. The novel antipsychotic cariprazine (RGH-188): State-of-the-art in the treatment of psychiatric disorders. *European Psychiatry*. 2016;33:S228.
- [79] Nemeth G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet* 2017; 389: 1103-13.
- [80] Davidson M, Saoud J, Staner C, Noel N, Luthringer E, Werner S et al. Efficacy and Safety of MIN-101: A 12-Week Randomized, Double-Blind, Placebo-Controlled Trial of a New Drug in Development for the Treatment of Negative Symptoms in Schizophrenia. *American Journal of Psychiatry*. 2017;174(12):1195-1202.
- [81] Morris RW, Quail S, Griffiths KR, Green MJ, Balleine BW. Corticostriatal control of goaldirected action is impaired in schizophrenia. *Biol Psychiatry* 2015; 77: 187-95.
- [82] Galderisi S, Färden A, Kaiser S. Dissecting negative symptoms of schizophrenia: History, assessment, pathophysiological mechanisms and treatment. *Schizophrenia Research*. 2017;186:1-2.
- [83] Trémeau F, Nolan K, Malaspina D, Javitt D. Behavioral validation of avolition in schizophrenia. *Schizophrenia Research*. 2012; 138(2-3):255-261.
- [84] Barch DM, Pagliaccio D, Luking K. Mechanisms underlying motivational deficits in psychopathology: similarities and differences in depression and schizophrenia. *Curr Topics Behav Neurosci* 2016; 27: 411-49.
- [85] Radua J, Schmidt A, Borgwardt S, et al. Ventral striatal activation during reward processing in psychosis: a neurofunctional meta-analysis. *JAMA Psychiatry* 2015; 72: 1243-51.
- [86] Beck A, Grant P, Huh G, Perivoliotis D, Chang N. Dysfunctional Attitudes and Expectancies in Deficit Syndrome Schizophrenia. *Schizophrenia Bulletin*. 2011; 39(1):43-51.
- [87] Grant P. Randomized Trial to Evaluate the Efficacy of Cognitive Therapy for LowFunctioning Patients With Schizophrenia. *Archives of General Psychiatry*. 2012;69(2):121-127.
- [88] Lindenmayer J, Nasrallah H, Pucci M, James S, Citrome L. A systematic review of psychostimulant treatment of negative symptoms of schizophrenia: Challenges and therapeutic opportunities. *Schizophrenia Research*. 2013;147(2-3):241-252.

- [89] Sethom M, Fares S, Bouaziz N, Melki W, Jemaa R, Feki M et al. Polyunsaturated fatty acids deficits are associated with psychotic state and negative symptoms in patients with schizophrenia. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2010;83(3):131- 136.
- [90] Tsapakis E, Dimopoulou T, Tarazi F. Clinical management of negative symptoms of schizophrenia: An update. Pharmacology & Therapeutics. 2015;153:135-147.
- [91] Ellman L, Cook A, Schaefer C, Bresnahan M, Susser E, Brown A. 113. Maternal inflammation during pregnancy and symptom profiles of offspring diagnosed with schizophrenia. Brain, Behavior, and Immunity. 2014;40:e33.
- [92] Oya K, Kishi T, Iwata N. Efficacy and tolerability of minocycline augmentation therapy in schizophrenia: a systematic review and meta-analysis of randomized controlled trials. Human Psychopharmacology: Clinical and Experimental. 2014;29(5):483-491.
- [93] Freitas C, Fregni F, Pascual-Leone A. Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. Schizophrenia Research. 2009;108(1-3):11-24.
- [94] Dlabač-de Lange J, Knegtering R, Aleman A. Repetitive Transcranial Magnetic Stimulation for Negative Symptoms of Schizophrenia. The Journal of Clinical Psychiatry. 2010;71(04):411-418.
- [95] Smith R, Boules S, Mattiuz S, Youssef M, Tobe R, Sershen H et al. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: A randomized controlled study. Schizophrenia Research. 2015;168(1-2):260-266.
- [96] Fitzgerald P, McQueen S, Daskalakis Z, Hoy K. A Negative Pilot Study of Daily Bimodal Transcranial Direct Current Stimulation in Schizophrenia. Brain Stimulation. 2014;7(6):813-816.
- [97] Cohen A, Morrison S, Brown L, Minor K. Towards a cognitive resource limitations model of diminished expression in schizotypy. Journal of Abnormal Psychology. 2012;121(1):109-118.
- [98] Lepage M, Sergerie K, Benoit A, Czechowska Y, Dickie E, Armony J. Emotional face processing and flat affect in schizophrenia: functional and structural neural correlates. Psychological Medicine. 2011;41(09):1833-1844.
- [99] Stip E, Fahim C, Liddle P, Mancini-Marie A, Mensour B, Bentaleb L et al. Neural Correlates of Sad Feelings in Schizophrenia with and without Blunted Affect. The Canadian Journal of Psychiatry. 2005;50(14):909-917.
- [100] Aleman A, Kahn R. Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? Prog. Neurobiol. 2005;77(5), 283-298.
- [101] Hager O, Kirschner, M, Bischof M, Hartmann-Riemer M, Kluge A, Seifritz E, Tobler P, Kaiser S. Reward-dependent modulation of working memory is associated with negative symptoms in schizophrenia. Schizophr. Res. 2015;168 (1-2), 238-244.
- [102] Bor J, Brunelin J, d'Amato T, Costes N, Suaud-Chagny M, Saoud M et al. How can cognitive remediation therapy modulate brain activations in schizophrenia?. Psychiatry Research: Neuroimaging. 2011;192(3):160-166.

- [103] Elis O, Caponigro J, Kring A. Psychosocial treatments for negative symptoms in schizophrenia: Current practices and future directions. *Clinical Psychology Review*. 2013;33(8):914-928.
- [104] De Berardis D, Marini S, Iasevoli F, Tomasetti C, deBartolomeis A, Mazza M, Valchera A. The role of intranasal oxytocin in the treatment of patients with schizophrenia: a systematic review. *CNS Neurol. Disord. Drug Targets*. 2013;12:252-264.
- [105] Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of general psychiatry*. 2003 Dec 1;60(12):1187-92.
- [106] Fanous AH, Van Den Oord EJ, Riley BP, Aggen SH, Neale MC, O'Neill FA, Walsh D, Kendler KS. Relationship between a high-risk haplotype in the DTNBP1 (dysbindin) gene and clinical features of schizophrenia. *American Journal of Psychiatry*. 2005 Oct 1;162(10):1824-32.
- [107] DeRosse P, Funke B, Burdick KE, Lencz T, Ekholm JM, Kane JM, Kucherlapati R, Malhotra AK. Dysbindin genotype and negative symptoms in schizophrenia. *American Journal of Psychiatry*. 2006 Mar 1;163(3):532-4.
- [108] Pelayo-Terán JM, Crespo-Facorro B, Carrasco-Marín E, Pérez-Iglesias R, Mata I, Arranz MJ, Leyva-Cobián F, Vázquez-Barquero JL. Catechol-O-methyltransferase Val158Met polymorphism and clinical characteristics in first episode non-affective psychosis. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 2008 Jul 5;147(5):550-6.
- [109] Wessman J, Paunio T, Tuulio-Henriksson A, Koivisto M, Partonen T, Suvisaari J, Turunen JA, Wedenoja J, Hennah W, Pietiläinen OP, Lönngqvist J. Mixture model clustering of phenotype features reveals evidence for association of DTNBP1 to a specific subtype of schizophrenia. *Biological psychiatry*. 2009 Dec 1;66(11):990-6.
- [110] Bertolino A, Fazio L, Caforio G, Blasi G, Rampino A, Romano R, Di Giorgio A, Taurisano P, Papp A, Pinsonneault J, Wang D. Functional variants of the dopamine receptor D2 gene modulate prefronto-striatal phenotypes in schizophrenia. *Brain*. 2009 Feb 1;132(2):417-25.
- [111] Petrovsky N, Quednow BB, Ettinger U, Schmechtig A, Mössner R, Collier DA, Kühn KU, Maier W, Wagner M, Kumari V. Sensorimotor gating is associated with CHRNA3 polymorphisms in schizophrenia and healthy volunteers. *Neuropsychopharmacology*. 2010 Jun;35(7):1429-39.
- [112] Xu C, Aragam N, Li X, Villla EC, Wang L, Briones D, Petty L, Posada Y, Arana TB, Cruz G, Mao C. BCL9 and C9orf5 are associated with negative symptoms in schizophrenia: meta-analysis of two genome-wide association studies. *PloS one*. 2013 Jan 29;8(1):e51674.
- [113] Mezquida G, Penades R, Cabrera B, Savulich G, Lobo A, González-Pinto A, Penzol MJ, Corripio I, Fernandez-Egea E, Gassó P, Cuesta MJ. Association of the brain-derived neurotrophic factor Val66Met polymorphism with negative symptoms severity, but not cognitive function, in first-episode schizophrenia spectrum disorders. *European Psychiatry*. 2016 Oct;38:61-9.
- [114] Edwards AC, Bigdeli TB, Docherty AR, Bacanu S, Lee D, De Candia TR, Moscati A, Thiselton DL, Maher BS, Wormley BK, Molecular Genetics of Schizophrenia Collaboration (MGS). Meta-analysis of positive and negative symptoms reveals

schizophrenia modifier genes.
Schizophrenia bulletin. 2016 Mar
1;42(2):279-87.

[115] Gao J, Yi H, Tang X, Feng X, Yu M, Sha W, Wang X, Zhang X, Zhang X. DNA methylation and gene expression of matrix metalloproteinase 9 gene in deficit and non-deficit schizophrenia. Frontiers in genetics. 2018 Dec 11;9:646.

[116] Schneider M, Armando M, Schultze-Lutter F, Pontillo M, Vicari S, Debbané M, Eliez S. Prevalence, course and psychosis-predictive value of negative symptoms in 22q11. 2 deletion syndrome. Schizophrenia research. 2019 Apr 1;206:386-93.