Behavioral outputs of negative symptom domains of schizophrenia

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Received March 1, 2021; Accepted March 31, 2021

DOI: 10.3892/etm.2021.10237

Abstract. The present study aimed to validate the hypothesis that negative symptoms of schizophrenia encompass two domains, namely avolition-apathy (AA) and diminished expression (DE), and to investigate the relationship of these domains with behavioral outputs which imply hedonic activities: Cigarette use and weight gain. A total of 106 consecutive schizophrenia outpatients with primary negative symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS), the Negative Symptoms Assessment Scale (NSA-16), the Calgary Depression Scale for Schizophrenia (CDSS), and the Simpson-Angus Scale (SAS). A semi-structured interview was used to assess demographic features, the number of cigarettes smoked per day, and body mass index. Data were analyzed using descriptive statistics, principal component analysis, analysis of variance, and covariance. A two-factor solution was revealed for the negative symptoms of schizophrenia represented by AA and DE. Analyses of variance and covariance suggested that higher AA scores were associated with normal weight and non-smoking status. No significant differences were revealed regarding DE scores in relationship with the same behavioral hedonic outputs. The present results indicated the AA and DE domains exhibit meaningful differences concerning the outcome, which may imply the need for different approaches regarding rating and treatment.

Introduction

Negative symptoms of schizophrenia are recognized to be a core feature of the disorder. They have been associated with detrimental effects on the long-term outcome and the quality of life of patients (1-5). There has been a recent focus on this category of symptoms due to the heterogeneity of the psychopathology of the domain and not yet controlled by current treatments (6).

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Key words: avolition-apathy, diminished expression, body mass index, smoking, schizophrenia

In 2006, the National Institute of Mental Health in MATRICS Consensus Statement on Negative Symptoms established a distinction between primary and secondary negative symptoms. The primary symptoms are a part of the disease itself, and the secondary ones are the results of extrapyramidal side-effects, depression, positive symptoms, or social deprivation. The same consensus discussed and validated the constitutive factors the negative domain: Blunted affect, alogia, asociality, anhedonia, and avolition (7).

More recent studies have shown that these symptoms can be grouped in two domains: Experiential deficit avolition-apathy (AA) consisting of asociality, anhedonia and avolition, and expressive deficit diminished expression (DE) consisting of blunted affect and alogia. This factorial solution emerged from factor analytic studies. However, it is unclear whether these symptoms can be fully reduced to this solution because the cognitive and neural bases are not fully understood (8-10).

Findings from neuroimaging studies support different etiologies for the two domains. Dysfunctions in the reward system are common mechanisms for all symptoms in the AA domain, but mechanisms underlying each symptom may also be present (11). On the other hand, for the DE domain, no common mechanisms have been described, but for each symptom, functional and structural brain modifications have been revealed (12,13).

The ventral tegmental area, the nucleus accumbens, caudate nucleus, the amygdala, and prefrontal brain regions, such as the medial and the lateral orbitofrontal cortex, and the dorsolateral prefrontal cortex, are the network of brain regions included in the reward system (14,15). The reward system is essential for perceiving pleasure and joy. A diminished hedonic experience will undermine motivation for goal-directed behavior thus suboptimal achievement of behavioral goals will result in attenuated reward experience (14). Therefore, the impairments of the reward system have been linked to anhedonia and avolition in schizophrenia (16,17).

Studies on reward mechanisms have brought to attention that there are two types of reinforcers: Primary reinforcers or innate, such as feeding and sexual drive, and secondary reinforcers such as monetary rewards or drug abuse. The difference between the two reward types is that primary reinforcers are more related to affect, whereas secondary reinforcers, as a learned association, are dependent on cognition. Meta-analyses have revealed that the ventral striatum is the brain area engaged in reward anticipation for a broad range of stimuli regardless of the reinforcer type (18,19).

Our study aimed to investigate the relationship between hedonic behavioral outputs and primary negative symptoms as a dimensional approach (i.e., AA and DE) in patients diagnosed with schizophrenia. Weight was used to measure the hedonic drive for food (primary reinforcer), smoking as a marker for addiction-related, acquired behavior (secondary reinforcer). Smokers and non-smokers, normal weight, and overweight were the two categories used for this study. Subjects with at least three years of continuous treatment with antipsychotics were included in order to reduce the heterogeneity of medication after the peak risk of weight gain (20). The subjects were all outpatients to control better environmental situations, such as hospitalization, that could restrict normal dietary, smoking and could lead to social deprivation. It was hypothesized that smokers in the overweight range have lower levels of negative symptoms in the AA domain and that there would be no difference regarding the scores on the DE domain between groups.

Patients and methods

Patients. A total of 106 patients diagnosed with schizophrenia, according to the International Statistical Classification of Diseases and Related Health Problems 10th edition (21), were recruited between July 2016 and July 2017 for our study. The Ethics Committee of 'Iuliu Hatieganu' University of Medicine and Pharmacy (Cluj-Napoca, Romania) approved this study (approval no. 477/22/10/2015). The procedures of the present study were thoroughly explained to each patient and in compliance with the Declaration of Helsinki of 2008. Informed consent was obtained from each patient before the study began.

Assessment instruments

Demographic features. A semi-structured interview was used to assess demographic data: Age, sex, age of onset, duration of the disease, number of admissions in the hospital, number of cigarettes smoked per day, and body mass index calculated as weight/height^2 (kg/m^2).

Clinical features. The Positive and Negative Syndrome Scale (PANSS) was used to assess the symptomatology of the disease. The PANSS has 30 items scored on a 7-point scale, with higher scores indicating more severe symptoms. It has three subscales assessing positive, negative, and general symptomatology (22).

The Negative Symptoms Assessment Scale (NSA-16) is composed of 16 items scored from 1 to 6, and a higher score indicates greater severity. The items are grouped according to 5 factors: Communication, emotion/affect, social involvement, motivation, and retardation (23).

The Calgary Depression Scale for Schizophrenia (CDSS) is a 9-items scale used for assessing depressive symptoms separate from positive, negative, and extrapyramidal symptoms in people with schizophrenia. Ratings of the items are defined according to operational criteria from 0-3 (24).

The Simpson-Angus Scale (SAS) is a 10-item scale designed to evaluate parkinsonian side effects related to neuroleptic medication use. The items are rated on a 5-point scale from 0 to 5, 0 indicating the absence of the condition, and 5 for the extreme form of the condition (25).

The treatment was as follows: For research purposes, equivalent doses of chlorpromazine across antipsychotic medication were employed. Doses equivalent to 100 mg/day of chlorpromazine were: 2 mg/day for risperidone, 5 mg/day for olanzapine, 75 mg/day for quetiapine, 60 mg/day for ziprasidone, and 7.5 mg/day for aripiprazole (26).

Study design. The present study is a cross-sectional observational study which included subjects diagnosed with schizophrenia, recruited from the Psychiatric Outpatients Hospital in Cluj-Napoca, fulfilling the following criteria: i) Men and women aged between 18 and 60 years; ii) patients who had at least four years of antipsychotic treatment; iii) patients who were stable from the point of view of the symptomatology for at least three months (for the last three months, patients had not been admitted to the hospital and did not require any change in their antipsychotic treatment); and iv) patients who had predominant negative symptoms (PANSS negative subscale >21). Subjects were excluded if during the evaluation, secondary negative symptoms were present including depressive symptoms (CDSS >4), extrapyramidal symptoms (SAS>4), positive symptoms (PANSS positive subscale >20) (27). A total of 148 patients were invited to participate from which 19 declined, and 23 did not fulfill the inclusion criteria.

Statistical analysis. Descriptive statistics were used for all the study variables: Mean and standard deviation (SD) for continuous variables and percentages for categorical variables, $P<0.05$ was considered to indicate a statistically significant difference. To establish the two-factor structure of negative symptomatology Principal Component Analysis (PCA) was conducted on the 5-factor scores of the NSA-16 scale, using varimax rotation and Kaiser normalization (28). The criteria for the number of factors extracted were eigenvalue >1.

For the next analyses, the subjects were divided into groups. The first two groups were smokers and non-smokers (a smoker was defined as a patient who was smoking at least five cigarettes per day every day, patients who occasionally smoked and or smoked <5 cigarettes per day were considered non-smokers); the second analyses divided the subjects according to their BMI: Overweight (BMI >25) and normal weight (BMI <25).

Independent one-way analysis of variance (ANOVA) was used to test group differences for each group (smokers and non-smokers, patients with normal weight and overweight) on AA and DE mean scores. In case of significant differences, one-way analyses of covariance (ANCOVA) were conducted to control for age, duration of the disease, and treatment in equivalent doses of chlorpromazine.

Results

Sample description. The socio-demographic and clinical characteristics of the patients are presented in Table I.

Negative symptom dimensions. The PCA performed on the five factors of the NSA-16 scale indicated a two-factor structure explaining 84% of the variance. The first factor consisted of communication, emotion/affect, motor retardation representing DE, and the second factor, AA, consisted of motivation and social withdrawal. The factor loadings are presented in

Table I. Sociodemographic and clinical characteristics of the sample (n=106).

A, General characteristics	n (%)
Sex	
Male	23 (21.70)
Female	83 (78.30)
Age, years, mean (SD)	41.18 (10.30)
Duration of the disease, years, mean (SD)	13.12 (7.40)
Treatment, equivalents of chlorpromazine, mean (SD)	291.15 (212.36)
B, Behavioral outputs	**n (%)**
Smokers/non-smokers, yes/no	
Smokers	58 (54.70)
Non-smokers	48 (45.30)
Weight, normal weight BMI <25/overweight BMI >25	
Normal weight	46 (43.40)
Overweight	60 (56.60)
C, Psychopathology	**n (%)**
PANSS, total, mean (SD)	70.81 (8.96)
PANSS, positive, mean (SD)	12.24 (3.33)
PANSS, negative, mean (SD)	24.70 (3.95)
NSA-16, mean (SD)	53.31 (7.95)
NSA-16, communication, mean (SD)	2.74 (0.76)
NSA-16, emotion/affect, mean (SD)	3.57 (0.78)
NSA-16, motor retardation, mean (SD)	3.35 (1.07)
NSA-16, social withdrawal, mean (SD)	3.20 (0.77)
NSA-16, motivation, mean (SD)	3.85 (1.07)
CDSS, mean (SD)	2.10 (0.70)
SAS, mean (SD)	1.45 (0.93)

PANSS, Positive and Negative Syndrome Scale; NSA-16, Negative Symptom Assessment Scale; CDSS, Calgary Depression Scale for Schizophrenia; SAS, Simpson Angus Scale.

Table II. None of the NSA-16 scale subscale scores loaded highly (<0.45) on more than one factor.

Cigarette use. With regard to the comparison between smokers and non-smokers, ANOVA on AA mean scores revealed a significant group effect [$F(1,104)=11.12$, $P=0.001$, $\eta p^2=0.10$] due to the presence of more severe AA scores in the non-smoker's group than in smokers. ANCOVA performed showed that there is a significant group effect on AA mean scores [$F(1,103)=10.53$, $P=0.002$, $\eta p^2=0.09$] even after controlling for treatment [$F(1,103)=0.05$, $P=0.80$, $\eta p^2=0.001$]. The results are presented in Table III.

The smoker and non-smoker groups did not differ on DE mean scores [$F(1,104)=0.165$, $P=0.658$, $\eta p^2=0.002$].

Weight. One-way ANOVA performed to determine whether there were differences between the mean scores of the AA domain between patients with normal weight and overweight revealed a significant group effect [$F(1,104)=4.36$, $P=0.039$, $\eta p^2=0.040$] due to the presence of more severe AA scores in the normal weight group than the overweight group.

Table II. PCA factor loadings for individual negative symptom scores on the NSA-16 scale.

NSA-16 symptoms	DE factor	AA factor
Communication	0.788	0.429
Emotion/affect	0.812	0.273
Motivation	-0.383	0.874
Social withdrawal	-0.561	0.766
Motor retardation	0.894	0.229
Eigenvalues	2.54	1.66
Percentage of variance	50.79%	33.23%

NSA-16, Negative Symptoms Assessment Scale; DE, diminished expression; AA, avolition-apathy.

Table III. ANCOVA results and descriptive statistics for AA mean scores by smoking groups and treatment.

	AA mean scores			
Smoking group	Observed mean	Adjusted mean	SD	N
Non-smokers	3.91	3.90	0.90	48
Smokers	3.34	3.34	0.85	58
Source	SS	Df	MS	F
Treatment	0.46	1	0.46	0.05
Smoking	8.13	1	8.13	10.53
Error	79.56	103	0.77	

R^2=0.10, Adj. R^2=0.08, Homogeneity of regression (F=0.01, P=0.90). AA, Avolition-apathy, SS, type III sum of squares; Df, degree of freedom; MS, mean square.

Table IV. ANCOVA results and descriptive statistics for AA mean scores by weight groups, duration of the disease and treatment.

	AA mean scores			
Weight group	Observed mean	Adjusted mean	SD	N
Normal weight	3.80	3.81	0.95	46
Overweight	3.43	3.44	0.86	60
Source	SS	Df	MS	F
Duration of the disease	0.03	1	0.03	0.04
Treatment	0.42	1	0.42	0.51
Weight	3.56	1	3.56	4.32
Error	84.14	102	0.82	

R^2=0.04, Adj. R^2=0.01, Homogeneity of regression (F=0.64, P=0.42). AA, Avolition-apathy, SS, type III sum of squares; Df, degree of freedom; MS, mean square.

ANCOVA performed revealed that there was a significant effect between groups on AA mean scores [F(1,102)=4.32, P=0.040, ηp^2=0.041] even after adjusting for duration of the disease [F(1,102)=0.40, P=0.843, ηp^2=0.000] and treatment [F(1,102)=0.519, P=0.473, ηp^2=0.005]. The AA mean scores and the adjusted mean score are presented in Table IV.

No significant difference was revealed on the DE mean score between patients with normal weight and overweight [F(1,104)=0.58, P=0.44, ηp^2=0.006].

Discussion

Consistent with previous findings, a two-factor solution for the broad range of negative symptoms, as assessed by the NSA-16 scale, was replicated through our analysis. The first factor included alogia, blunted affect, and motor retardation and represented the DE. The second factor consisted of social withdrawal and motivational deficits indicating the experiential deficit (AA) (4,7,9,17,29,30).

Sustaining the initial hypothesis, lower scores of the AA domain were associated with smoking and normal weight. The scores of the DE domain did not differ between the subject groups.

Tobacco use among patients with schizophrenia revealed high rates, more than three times higher than in the general population, with a prevalence of 72-90% of smokers in this population (31). The cardiovascular and pulmonary risks and the economic burden have drawn attention to the underlying mechanism of the increased rates of smoking among this category of patients (32). In line with previous studies, the present research revealed that lower rates of negative symptoms were associated with nicotine use (33,34). The AA dimension of the negative symptomatology had significantly lower scores in the tobacco users group. Several hypotheses have been proposed to explain the reduced negative symptomatology association with nicotine use. It has been revealed that nicotine increases dopamine levels in the brain, whereas negative symptoms are related to a hypo-dopaminergic state. Therefore the effects of smoking may be related to the small amount of nicotine produced by the cigarette (33,35). Supporting this theory, several studies have revealed a worsening of positive symptoms and the use of higher doses of antipsychotic medication in smokers (33,35). In addition, it has been hypothesized that nicotine reduces dopamine degradation and enhances the effects of nicotine-mediated dopamine release in the mesocortical pathways, which results in cognition improvement and the

decrease of negative symptoms (35). All these theories emerge from the assumption that nicotine ameliorates the negative symptoms, but another point of view is that nicotine may ameliorate deficits existing in the reward system (36-38). This could explain the differences between the negative symptom domains concerning tobacco use and why smokers present lower apathy-avolition levels. Furthermore, the dysfunctions of the reward system underlying the AA domain could be responsible for the non-smoking behavior, considering that smoking is an acquired salient behavior (39). Several limitations of the present study have to be mentioned here: The smoking status was self-reported, which could be a potential source of bias, and the results were controlled only for doses of treatment as equivalents of chlorpromazine, not for the administered type of drugs.

Overweight and obesity in schizophrenia are severe and frequent complications widely attributed to the side effects of the medication although a dose-dependent effect has not been demonstrated (40). Several other factors have been incriminated for obesity in patients with schizophrenia besides the medication-related ones (the type of medication and treatment duration), for example, the severity of the illness, lifestyle, and low socioeconomic status. Olanzapine and clozapine have been demonstrated to be most obesogenic among antipsychotics, although it should be mentioned that clozapine is used for treatment-resistant schizophrenia, which may imply a relationship between weight gain and severity of the illness (41). A meta-analysis from 2010 correlated the effectiveness of antipsychotic drugs with weight gain (42). Other studies have revealed a significantly higher prevalence of overweight in drug naïve patients with schizophrenia (43). These data indicated that weight gain in patients with schizophrenia is linked to medication and the severity of the psychopathology. An association between weight gain and higher levels of negative symptoms has been proposed due to the motivational deficit, leading to decreased physical activity (44-46). Conflicting with previous studies, our results revealed that higher scores in AA were present in patients with normal weight, and the DE scores did not significantly differ between normal and overweight subjects. Two previous studies were revealed sustaining our hypothesis (47,48), but neither of these studies investigated the relationship between weight gain and the domains of negative symptomatology. In our attempt to control medication as a confounding factor, inclusion criteria were established for patients to be on continuous medication for at least four years, as it is accepted that antipsychotic medication-induced weight gain plateaus after approximately three years of continuous treatment (49). However, the heterogeneity of the treatment remains a limitation of our study. Even after controlling for the treatment dose, calculated in equivalent doses of chlorpromazine and for the duration of the disease, the difference between groups remained significant: Overweight patients presenting lower scores on AA. This association may be attributed to the dysfunctions in the reward system, which underlies the AA symptomatology (47).

Further brain imaging investigations are required to establish this relationship. To date, functional brain imaging studies have reported conflicting results on this matter: Some revealed a hyperreactivity while others hyporeactivity in the reward system in obese patients while being shown appetizing cues (50-53). A different possible interpretation of our results is that the hedonic and motivational deficit implies an impaired daily functioning, including food preparation, which may lead to a lack of weight gain.

Our findings extend previous studies regarding AA and DE domains, supporting the evidence that these domains should be considered distinct psychopathological domains and should be approached separately in terms of evaluation, treatment, and prognosis.

The present study explored the association between negative symptom domains and weight gain, smoking as behavioral outputs of hedonic experiences. The present findings established an association behavioral hedonic outputs with lower apathy and avolition symptoms, but not with the expressive dimension, in patients with schizophrenia. Higher avolition and asociality symptom severity scores were present in patients with lower BMI who were not smoking. Although our results revealed reduced AA symptoms among smoking and overweight patients with schizophrenia, clinicians should encourage smoking cessation and strategies preventing weight gain because obesity and smoking have high morbidity and mortality rates. Thitherto, as aforementioned there are several theories proposed for the underlying mechanisms to support these associations, but this relationship does not imply causation and even though negative symptoms represent a substantial impediment in overall functioning the same importance should be attributed to the cardiovascular risk emerging from obesity and smoking.

In conclusion, our results support the evidence that AA and DE domains warrant separate approaches concerning causal and behavioral models, as well as short- and long-term clinical approaches.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors contributed to the study conception and design as well as the material preparation, data collection and statistical analysis. The first draft of the manuscript was written by OC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved (approval no. 477/22/10/2015) by the Ethics Committee of 'Iuliu Haţieganu' University of Medicine and Pharmacy (Cluj-Napoca, Romania). Informed consent was obtained from each patient prior to the start of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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