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Šagud, Marina; Tudor, Lucija; Šimunić, Lucija; Jezernik, Dejana; Madžarac, Zoran; Jakšić, Nenad; Mihaljević Peleš, Alma; Vuksan-Ćusa, Bjanka; Šimunović Filipčić, Ivona; Stefanović, Ivana; ...

Source / Izvornik: **Suicide and Life-Threatening Behavior, 2021, 51, 446 - 454**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1111/sltb.12724

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:455292

Physical and social anhedonia are associated with suicidality in major depression but not in schizophrenia

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Introduction

Anhedonia, the difficulty in experiencing pleasure from pleasurable experiences, affects many areas of life. It includes physical anhedonia (PA), an inability to feel physical pleasure, and social anhedonia (SA), a diminished capacity for pleasure in social activities (Chapman et al., 1976). Anhedonia might occur in any population, but it is far more common in individuals

with psychiatric disorders (Sagud et al., 2019). According to the DSM-5 criteria (American Psychiatric Association, 2013), anhedonia is a hallmark of major depressive disorder (MDD) and also a negative symptom in schizophrenia.

Suicidal ideation, attempts and completed suicides are among the worst complications in psychiatry, and there is an urgent need to establish clinical features related to high suicidal risk. Such risks might comprise anhedonia, which predicted suicidality in psychiatric patients (Winer et al., 2014). There are greater anhedonia levels in population with higher suicidal ideation, with or without psychiatric disease (Ducasse et al., 2018). Most studies focused on current suicidality, without addressing suicide attempt history (Ducasse et al., 2018; Winer et al., 2014), although suicide attempts were among the strongest risk factors for future suicide deaths (Simon et al., 2018). Greater anhedonia levels are found in suicide attempters, at least in adolescents (Auerbach et al., 2015). While only a minority of articles addressed PA with respect to suicidal ideation (Ducasse et al., 2018), none measured SA in the context of life-time suicide attempts. There are few data on the relationship between suicidality and PA in schizophrenia. (Loas, Azi, Noisette, Legrand, & Yon, 2009). The simple relationship between suicidality and anhedonia does not exist, due to the high complexity of these conditions. Both higher and lower anhedonia levels were repeatedly associated with suicidal behavior (Bonanni et al., 2019; Loas, 2014). Therefore, this relationship should be viewed according to the different typres of suicidal behavior, such as suicidal ideation (recent or life-time), suicide attempt (recent or life-time) and suicidal plan. Based on the literature gap on different aspects of suicidality and PA, and particularly SA, in psychiatric patients, this study has focused on the relationship between PA and SA and recent suicidal ideation and life-time suicide attempts, in healthy, depressive (melancholic and non-melancholic) and schizophrenia (deficit and non-deficit) patients.

Method

Participants and procedure

Patients with MDD (N=178) or schizophrenia (N=312) were recruited at the Department of Psychiatry, University Hospital Centre Zagreb, and diagnosed by a structured clinical interview (First et al., 1995) based on the DSM-IV criteria (American Psychiatric Association, 1994). Non-psychiatric controls (controls; N=193) were enrolled in the Health Centre Slavonski Brod, during regular medical screening. All participants met the following inclusion: (1) signed the informed consent document, approved by the Ethics Committees of both institutions (2) age between 18 and 65 years, (3) sufficient capacity to read and understand self-rating questionnaires, and exclusion criteria: (1) any neurological condition that could influence hedonic capacity, such as Parkinson disease; (2) no recent (less than 3 months ago) alcohol or psychoactive drug abuse or dependence. Exclusion criteria for both patient groups was the absence of severe disease symptoms, which would preclude the cooperation during testing. Exclusion criteria only for the controls was a negative psychiatric history and the use of psychotropic drugs (except occasional use of benzodiazepines or hypnotics).

Measures

Patients with MDD completed the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). Patients with schizophrenia were rated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1996). Controls were rated by the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001; Kroenke, Spitzer, & Williams, 2001). Anhedonia was assessed by the revised PA Scale (RPAS) and with the revised SA scale (RSAS), (Chapman et al., 1976). Participants were considered to have PA if they had RPAS scores >20 in women and >28 in men, whereas the cut-off scores for SA were >16 in women and >20 in men (Kwapil et al., 2002). Suicide attempt history was recorded by psychiatric interviews and from medical records. Recent suicidal ideation was evaluated using

MADRS item 10 in MDD patients, CDSS item 8 in schizophrenia patients, and PHQ-9 item 7 in controls. Patients with MDD were separated as melancholic (having MADRS item 1≥6, or item 8≥2 (Peters et al., 2018) or non-melancholic groups. Schizophrenia patients were devided by the PANSS-derived proxy for the deficit syndrome to distinguish deficit vs. nondeficit patients, using the formula: (n1+n4)–(p7+g2+g3+g6) = (blunted affect+passive/apathetic social withdrawal) – (hostility+anxiety+guilt feelings+depression). Patients with scores from −1 to 1 were assigned to the deficit group (N = 21); while others (with scores from −2 or lower) were assigned to the nondeficit group (Kirkpatrick et al., 2019).

Data analysis

Statistical analysis was performed on Sigma Stat. The normality of data was assessed with the Kolmogorov-Smirnov test. Since most of the tested variables deviated from normality, non-parametric statistical tests were used: Mann Whitney test for testing the differences between 2 groups, or for 3 or more groups, Kruskal-Wallis ANOVA followed by Dunn's test. Stepwise multiple linear regression was used to examine the effect of several covariates on suicidality. The correlation was tested with the Spearman's rank of correlation. Differences in the distributions were assessed with a χ^2 test. P-value was set to 0.05. Before the study, G*Power 3 Software was used to determine the required sample size and statistical power. With p=0.05; and medium effect size=0.15, 0.25 or 0.5; and power $(1 - \beta) = 0.800$; for the stepwise multiple linear regression, the required sample size was 92; for χ^2 test with df=1; the required sample size was 88; for the Mann-Whitney test, the required sample size was 128; and for the Kruskal-Wallis ANOVA, the required sample size was 159. Since the study included 683 participants, it had an adequate sample size and statistical power to detect significant differences across the groups.

Results

Group characteristics are presented in Table 1. Patients with MDD had more frequently PA ($p<0.001$) and SA ($p<0.001$) than participants with schizophrenia or controls. Patients with MDD had higher RPAS ($p=0.003$) and RSAS ($p<0.001$) scores than schizophrenia patients who had higher RPAS ($p=0.001$) and RSAS ($p=0.021$) scores than the controls. Patients with MDD and schizophrenia had similar ($p=0.117$) distribution (χ^2 test) of participants with the life-time suicide attempts. No past suicide attempts were recorded in controls.

Stepwise multiple linear regression was used to determine the effects of sex, age, past suicide attempt(s), therapeutic dose and smoking on the RPAS and RSAS scores in patient groups. The model was significant in MDD group for the RPAS ($p=0.011$) and RSAS ($p=0.020$) scores, and in schizophrenia group for the RPAS scores ($p=0.009$). In MDD patients, significant predictors of PA severity were age ($p=0.042$) and higher antidepressant dose ($p=0.048$) while the only predictor of SA severity was the presence of life-time suicidal attempts ($p=0.018$). In schizophrenia group, sex ($p=0.002$) and age ($p=0.030$) contributed to the PA severity.

In patients with MDD, highly positive correlation was observed between the MADRS and RPAS ($\rho=0.389$; $p<0.001$) or RSAS ($\rho=0.437$; $p<0.001$) scores, as well as between the RPAS and RSAS ($\rho=0.684$; $p<0.001$) scores. The total MADRS ($U=2661.0$; $p=0.081$) scores did not differ significantly between groups with positive or negative life-time suicide attempt history. In controls, the PHQ scores correlated significantly with the RPAS ($\rho=0.283$; $p<0.001$) and RSAS ($\rho=0.372$; $p<0.001$) scores, and the RPAS and RSAS scores were also highly correlated ($\rho=0.502$; $p<0.001$). In schizophrenia patients, the RPAS scores significantly correlated with the PANSS ($\rho=0.292$; $p<0.001$) and the CDSS ($\rho=0.224$; $p<0.001$) scores, and RSAS scores were significantly correlated with the total PANSS ($\rho=0.381$; $p<0.001$) and CDSS ($\rho=0.330$; $p<0.001$) scores.

To evaluate the association between suicidality and anhedonia, patients were grouped into 1) those with PA and SA; 2) with or without life-time suicidal attempts; and 3) with or without recent suicidal ideation (Table 2). Among MDD patients, the frequency (χ^2 test) of participants with life-time suicidal attempts was similar irrespective of the presence of PA (p=0.511), while more life-time suicide attempters (36.5%) had SA than non-attempters. Patients with PA (p=0.012) and SA (p<0.001) with recent suicidal ideation had significantly higher median MADRS-item 10 score than patients without the PA or SA (Table 2). This substantial relationship was confirmed by the correlation between the MADRS-item 10 score and the RPAS (ρ=0.241; p=0.001) and RSAS scores (ρ =0.372; p<0.001). Life-time suicide attempters had higher RPAS (U=2508.0; p=0.025) and RSAS (U=2295.0; p=0.003) scores than non-attempters.

Patients with MDD were separated into groups with (N=133) and without (N=45) melancholic features. Patients with melancholia had significantly higher RPAS (U=2039.0; p=0.001) and RSAS (U=2053.5; p=0.002) scores than patients without melancholia. Melancholic patients more often had PA (81.7%) than non-melancholic (68.8%) patients (χ^2=3.391; p=0.047), and more frequently SA (83.8%) than non-melancholic (68.3%) patients (χ^2=5.509; p=0.019).

There were no significant differences in the prevalence of melancholia between previous life-time suicide attempters and non-attempters (χ^2=1.027; p=0.311). Two-way ANOVA evaluated the effects of PA or SA and melancholic depression and their interaction on recent suicidal ideation (MADRS item 10). There was a highly significant association of melancholic depression with MADRS item 10 scores (F=14.596; p<0.001). However, main effect of PA (F=2.747; p=0.099) and joint effect of PA and melancholic depression (F=0.172; p=0.679) were not significantly associated with MADRS-10 score. Similarly, significant main effects of SA (F=4.895; p=0.028) and melancholic depression (F=14.919; p<0.001), and a lack of their interaction (F=1.808; p=0.181) on MADRS item 10 were observed.

Patients with schizophrenia with or without PA (p=0.498) and SA (p=0.224) had similar frequency of participants with life-time suicide attempts, and similar median CDSS-item 8 score (p=0.220 and p=0.417, respectively) (Table 2). Life-time suicide attempters and non-attempters had similar PANSS (U=8110.0; p=0.777), CDSS (U=7273.5; p=0.113), RPAS (U=7772.5; p=0.426) and RSAS (U=8241.5; p=0.934) total scores. Patients with deficit schizophrenia (N=192) had significantly lower RPAS scores (U=9185.0; p=0.003) than patients with non-deficit schizophrenia (N=120), while the RSAS scores were similar (U=10227.5; p=0.095). However, patients with non-deficit schizophrenia more frequently ($\chi2$=4.542; p=0.033) had SA (50.9%) than patients with deficit schizophrenia (35.7%), and similar trend was found regarding PA ($\chi2$=3.621; p=0.057). There were no significant ($\chi2$=0.271; p=0.603) differences in the frequency of life-time suicide attempters and non-attempters between deficit and non-deficit schizophrenia patients. Two-way ANOVA with a deficit syndrome and PA as fixed factors showed significant main effect of deficit syndrome on CDSS current suicidal ideation scores (F=8.726; p=0.003), while the main effect of PA (F=0.079; p=0.779) and their interaction (F=0.179; p=0.672) were not significantly associated with CDSS item 8 score. Similar results were observed with deficit syndrome and SA placed as fixed factors. Main effect of deficit syndrome was significantly associated with current suicidal ideation (F=7.040; p=0.008), while SA (F=0.137; p=0.711) and interaction of SA and deficit syndrome did not show significant association (F=0.067; p=0.796).

Discussion

Our main finding was the robust association of PA and SA with suicidality in MDD patients, and the lack of such relationship in schizophrenia. The associations of recent suicidal ideation with the presence and severity of anhedonia in MDD patients agree with other reports, though anhedonia, depressive symptoms, and suicidality were assessed by different tools. Anhedonia

was associated with suicidal ideation severity in treatment-resistant MDD patients (Ballard et al., 2017), participants with depressive spectrum disorders (Spijker et al., 2010) and those with different diagnoses, including affective disorders (Yaseen et al., 2016), while suicidal ideation was associated with decreased motivation to experience pleasure in MDD outpatients (Xie et al., 2014).

We also observed the association between life-time suicide attempts and anhedonia severity in MDD, which is also in line with the most studies (Loas et al., 2000; Zielinski et al., 2017). While PA was related to completed suicide during follow-up after suicide attempts (Loas, 2007), in another prospective study, anhedonia was a predictor of completed suicide 13 months later (Fawcett et al., 1990). Our MDD patients with life-time suicide attempts had similar depression severity, but more frequently SA than non-attempters, implicating that SA, rather than depression intensity, deserves further investigation as a potential risk factor for suicidality. Moreover, the presence of melancholia was associated with both anhedonia and recent suicidal ideation, but not with the existence of life-time suicide attempts. Likewise, MDD subjects with melancholia had more suicidal ideation, but the proportion of patients with suicidal acts was similar to those without melancholia (Tondo et al., 2020). Melancholia and SA independently contributed to current suicidal ideation, which suggests that screening MDD patients for both melancholia and SA might help detecting those with suicidal ideation.

In the present trial, the higher antidepressant dose predicted PA, which might be unexpected, because antidepressants are supposed to treat anhedonia. While patients with anhedonia had higher depression scores, they might be given greater antidepressant dose due to more severe symptoms and/or treatment non-response. A recent meta-analysis reported that anhedonia might be related to poor response to antidepressants (Noma et al., 2019). Patients with treatment-resistant MDD had higher severity of anhedonia, suicidal ideation (Sternat et al., 2018), and a greater number of past suicide attempts (Sagud et al., 2013) than non-treatment

resistant individuals. While we did not address treatment-resistance, anhedonia might contribute to the suicidal behavior in these patients.

We detected no association between the presence/severity of anhedonia and life-time suicidal attempts/current suicidal ideation in schizophrenia patients. This is in line with the lack of a direct association between motivation and pleasure scores and recent suicidal ideation in patients with schizophrenia or schizoaffective disorder (Jahn et al., 2016). In contrast, suicide completers with schizophrenia had higher baseline PA than patients who died from other causes (Loas et al., 2009). Different relationships between anhedonia and suicidality among MDD and schizophrenia groups in our study might arise from various illness severities, age and/or treatment effects, and distinct biological background of anhedonia. Age contributed to the severity of PA in our patient groups. Since schizophrenia patients were younger, older patients might have greater PA scores. Our MDD respondents were moderately ill, while schizophrenia patients were remitted, or mildly ill. Therefore, the relationship between suicidal ideation and anhedonia might change if psychotic symptoms become more prominent.

In contrast to previous data, our patients with non-deficit schizophrenia had higher RPAS scores (Loas et al., 1996). Divergent results might be explained by the criteria for deficit schizophrenia, such as BPRS items (Loas et al., 1996) vs. PANSS derived proxy (present study) which is less restrictive definition (Kirkpatrick et al., 2019; Loas et al., 1996). The same group reported no correlation between the RPAS and PANSS negative score in another report (Loas et al., 1996). It might be that patients with deficit schizophrenia are less aware of their anhedonia, given that anhedonia is a subjective experience. While Chapman's scales measure hypothetical self-reports of positive emotions, which requires semantic memory (Strauss and Gold, 2012), patients with deficit schizophrenia had more severe cognitive impairment, including increased false-memory creation than non-deficit patients (Kanchanatawan et al., 2018). Moreover, schizophrenia patients might not be unable to experience pleasure, but,

instead, have reduced expectations, or too few pleasurable events to remember, because they spend much of their time alone, even when being in remission (Myin-Germeys et al., 2018). Lastly, more than 80% of our patients with schizophrenia were not anhedonic, while the majority (62%) had deficit schizophrenia. Our findings agree with the presumption that anhedonia might not be a negative symptom of schizophrenia (Loas et al., 1996), at least it's consummatory type, presented as PA and SA.

Despite overlap in the neural substrates of anhedonia across diverse samples (Sharma et al., 2017; Zhang et al., 2016), anhedonia in schizophrenia might also be related to specific neurobiological findings, such as reduced ventral striatal activity (Arrondo et al., 2015). Some antipsychotics might also induce secondary negative symptoms, including anhedonia (Heinz et al., 1998). Unlike typical antipsychotics, including haloperidol, olanzapine might have beneficial effects on anhedonia (Juckel et al., 2006), while quetiapine had dose-dependent effects (Berger et al., 2008). Those findings must be also viewed within the context of several anhedonia dichotomies. Namely, differences might occur between consummatory and anticipatory anhedonia (Loas, 2014), with PA more strongly correlated with consummatory, than with anticipatory anhedonia (Gard et al., 2006). Anhedonia might also be a current disease symptom, but also a trait within a personality (Loas and Pierson, 1989). Trait anhedonia, i.e. life-long inability to experience pleasure, might be further reffered to as SA and PA (Chapman et al., 1976; Loas, 2014). A distinction between chronic anhedonia and recent changes was suggested, which are not captured by Champman's anhedonia scales (Winer et al., 2014). Despite the high correlation between PA and SA in our and other samples, they measure different anhedonia domains, with PA considered more promising for the research in schizophrenia, because items in SA might be more subjected to social pressure (Chapman et al., 1976). Moreover, the recent loss of interest, an item from „anhedonia subscale“ on the Beck

Depression Inventory-II, was predictive of suicidality, while the loss of pleasure was not (Winer et al., 2014).

Limitations of the study include cross-sectional design, which precludes the causality assessment. Early life-stressors, that might have contributed to the development of anhedonia (Bolton et al., 2018) were not assessed. Only PA and SA were evaluated, while patients with MDD and schizophrenia differ regarding consummatory and anticipatory anhedonia, which might be state markers in MDD, but trait markers in schizophrenia (Li et al., 2015), though all types of anhedonia were strongly correlated (Fortunati et al., 2015). Symptoms of depression were measured by different rating scales depending on the particular study group. Strengths involve sufficient sample size and inclusion of samples from homogeneous Caucasian population, thus preventing potential cultural differences in anhedonia, which were reported across different cultures (Daghigh et al., 2019).

In summary, anhedonia, while representing important treatment target in both MDD and schizophrenia, plays a different role in suicidality in those disorders. In MDD patients, both PA and SA were associated with the past and present suicidality, and should be taken into account while assessing suicidal risk. Future studies, using different scales to capture distinct anhedonia features in the same sample, are expected to more precisely detect which anhedonia subtypes are related to suicidal risks in various psychiatric disorders.

Acknowledgments

The study was supported partly by the project funded by the University of Zagreb: Biomarkers of therapeutic response in schizophrenia, project code: BM106. The funding source had no further role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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Table 1. Sociodemographic data, presented as median (25^{th}-75^{th} percentile) or frequency for each diagnostic group

	Diagnosis			
	Controls (N=193)	MDD (N=178)	Schizophrenia (N=312)	Statistics

Age (years)	42 (33-53)	54 (50-61)	42 (35-51)	H=101.069; df=2; p<0.001
Sex				χ^2=52.087;
Male	37.3%	28.1%	60.4%	df=2;
Female	62.7%	71.9%	33.6%	p<0.001
Level of education				χ^2=8.282;
Elementary	9.4%	16.3%	9.3%	df=4;
Secondary/High school	62.8%	58.4%	67.6%	p=0.082
University	27.7%	25.3%	23.1%	
Symptom severity (total score)	PHQ 6 (3-10)	MADRS 20 (14-28)	PANSS 68 (59-79)	-
Dose of psychotropic agents (mg / day) [a]	-	23.6 (14.0-37.3)	550.0 (367.5-862.5)	-
Illness duration (years)	-	14 (7-23)	18 (11-26)	-
Life-time suicide attempts	-			χ^2=2.454; df=1; p=0.117
Yes		28.1%	21.8%	
No		71.9%	78.2%	
Recent suicidal ideation (PHQ-9/MADRS-10/CDSS-8)	0 (0,0)	1 (0,2)	0 (0,0)	-
Current smoking				χ^2=0.720;
Yes	46.6%	47.8%	50.3%	df=2; p=698
No	53.4%	52.2%	49.7%	

Physical anhedonia (RPAS scores)	15 (11-20)	22 (15-28)	18 (13-23)	H=37.979; df=2; p<0.001
Physical anhedonia				χ^2=45.074;
Yes	16.6%	46.1%	23.4%	df=2;
No	83.4%	53.9%	76.6%	p<0.001
Social anhedonia (RSAS scores)	10 (7-14)	15 (10-21)	12 (7-17)	H=45.907; df=2; p<0.001
Social anhedonia				χ^2=52.653;
Yes	11.9%	41.6%	18.3%	df=2;
No	88.1%	58.4%	81.7%	p<0.001

[a] fluoxetine equivalents for patients on antidepressants, and chlorpromazine equivalents for patients on antipsychotics; H: Kruskal-Wallis ANOVA on ranks value; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder; PANSS: Positive and Negative Syndrome Scale; PHQ-9: Patient Health Questionnaire-9; RPAS: revised PA scale; RSAS: revised SA Scale; χ^2: chi-square

Table 2. The association between PA or SA with or without life-time suicide attempt(s) and recent suicidal ideation in patients with MDD and schizophrenia.

	Diagnosis			
	MDD (N=178)		Schizophrenia (N=312)	
	Life-time suicide	Recent suicidal ideation (MADRS-10)	Life-time suicide	Recent suicidal

		attempts Yes/No		attempts Yes/No	ideation (CDSS-8)
Physical anhedonia	Yes	30.5%/69.5%	1 (0,2)	24.7%/75.3%	0 (0,0)
	No	26.0%/74.0%	0 (0,2)	20.9%/79.1%	0 (0,0)
	Statistics	χ^2=0.433; p=0.511	U=3130.0; p=0.012	χ^2=0.458; p=0.498	U=8372.0; p=0.220
Social anhedonia	Yes	36.5%/63.5%	1 (0,2)	15.8%/84.2%	0 (0,0)
	No	22.1%/77.9%	0 (0,1)	23.1%/76.9%	0 (0,0)
	Statistics	χ^2=4.421; p=0.036	U=2550.0; p<0.001	χ^2=1.476; p=0.224	U=7055.5; p=0.417

Recent suicidal ideation was determined with the MADRS item 10 or the CDSS item 8 in patients with MDD or schizophrenia, respectively. Data are presented as frequency (%) or median (25^{th}-75^{th} percentile) for both diagnostic groups. Statistics: chi-square (χ^2) for frequency and Mann-Whitney test for suicidal scores. CDSS: Calgary Depression Scale for Schizophrenia; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder.