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ANHEDONIA IN THE PSYCHOSIS RISK SYNDROME: STATE AND TRAIT CHARACTERISTICS

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SUMMARY

Background: *Previous studies reported deficits in pleasure experience in schizophrenia, but little is known about anhedonia in psychosis risk syndrome. Aim of this study was: (1) to assess anhedonia in distinct help-seeking subgroups of young people identified through the Ultra-High Risk (UHR) criteria, (2) to explore its association with functioning and psychopathology in the UHR group, and (3) to monitor longitudinally its stability in UHR individuals along 1-year follow-up period.*

Subjects and methods: *All participants (78 UHR, 137 with a First Episode Psychosis (FEP), and 95 non-UHR/FEP), aged 13-35 years, completed the Comprehensive Assessment of At-Risk Mental States (CAARMS), the Beck Depression Inventory-II (BDI-II), the Schizotypal Personality Questionnaire - Brief version (SPQ-B), the Brief O-LIFE questionnaire (BOL), and the World Health Organization Quality of Life - Brief version (WHOQOL-BREF). We adopted two different indexes of anhedonia: i.e. CAARMS "Anhedonia" item 4.3 and BOL "Introvertive Anhedonia" subscale scores.*

Results: *In comparison with non-UHR/FEP, UHR individuals showed higher baseline CAARMS item 4.3 and BOL "Introvertive Anhedonia" subscale scores. No difference in anhedonia scores between UHR and FEP patients was found. After 1-year follow-up period, UHR subjects had a significant decrease in severity exclusively on CAARMS item 4.3 subscore.*

Conclusions: *In the UHR group, CAARMS anhedonia showed significant correlations with functioning deterioration, negative symptoms, and comorbid depression (including suicide ideation), while BOL anhedonia with a poorer self-perceived quality of life and specific schizotypal personality traits (i.e. interpersonal deficits and disorganization). Anhedonia is prominent in the psychosis risk syndrome and its severity is indistinguishable from that of FEP patients.*

Key words: *anhedonia - negative symptoms – depression - ultra high risk - early psychosis*

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INTRODUCTION

Anhedonia is traditionally defined as a reduced ability to feel pleasure and has been considered a core symptom of schizophrenia and/or a marker of vulnerability within the construct of schizotypy (Pelizza & Ferrari 2009). However, the validity of this conceptualization in schizophrenia has been recently questioned by modern laboratory-based studies on hedonic response to pleasant stimuli. Specifically, while the psychometric assessment of noncurrent hedonic experiences (based on retrospective self-reported questionnaires) suggested that patients with schizophrenia had lower levels of pleasure in comparison with healthy individuals (Pelizza et al. 2012), recent meta-analyses on current pleasant feelings in laboratory-based research found comparable valence and arousal in relation to pleasant stimuli between the two groups (Llerena et al. 2012). This "emotional paradox" of current and noncurrent pleasure experience has dimmed what anhedonia actually reflects in schizophrenia (Strauss et al. 2018). Thus, studies on young people at an early phase of the disorder (such as individuals at Ultra-High Risk (UHR) of psychosis) may provide further information on how and when this emotional deficit arises in schizophrenia.

Anhedonia in UHR individuals

Another paradox recently emerged in this field, relating to the new empirical evidence that, along the clinical staging of psychosis (Yung et al. 2005), the hedonic ability appears to be more intact in patients with schizophrenia, while is impaired in UHR subjects. Indeed, the psychometric approach based on self-reported noncurrent anhedonia (i.e. using trait questionnaires such as the Chapman's Anhedonia Scales) (Chapman & Chapman 1978, Eckblad et al. 1982) found high levels of inability to feel pleasure in UHR individuals (Jhung et al. 2016). This psychopathological feature has been considered as a risk factor for social impairment and as a latent vulnerability for schizophrenia-spectrum disorders (Strauss et al. 2018), being a potential predictor of transition to

psychosis (Velthorst et al. 2009). This hypothesis is further supported by the empirical evidence that trait anhedonia is an enduring phenotype correlated to schizotypy in nonclinical populations (Pelizza et al. 2012).

Differently from what reported in patients with schizophrenia, preliminary laboratory-based studies found significantly less positive emotion to pleasant stimuli and less negative emotion to unpleasant stimuli in UHR individuals than in healthy controls (Yee et al. 2010; Schlosser et al. 2014; Jhung et al. 2016). Several factor could be involved in this anhedonia paradox, including (a) the frequent comorbid presence of depression and anxiety in UHR subjects (Gruber et al. 2018), with anhedonia more generally reflecting the severity of the psychopathological picture rather than being specific for the psychotic risk (Fusar-Poli et al. 2014, Schultze-Lutter et al. 2015), and (b) the possible normalizing effect of antipsychotics (used in patients with psychosis more frequently than in UHR subjects) on hedonic response and rewarding process, with reduced hedonic ability in UHR individuals reflecting a more dysregulated dopaminergic neurotransmission (Strauss et al. 2018). Thus, whether pleasure experiences are intact or altered in people at UHR of psychosis remains an important empirical and clinical topic that needs further examination (Jhung et al. 2016).

Considering that available evidence is mainly based on cross-sectional studies on mixed adolescent/young adult UHR clinical samples, possible psychopathological dynamics could be revealed assessing anhedonia longitudinally (including the presence of variable [state-like] and/or stable [trait-like] components of the inability to feel pleasure in people at UHR of psychosis). Thus, the aim of the present study was three-fold: (a) to assess anhedonia levels in distinct help-seeking subgroups of adolescents and young adults identified through the UHR criteria (i.e. non-UHR vs. UHR vs. First Episode Psychosis [FEP]) (Yung et al. 2005); (b) to monitor longitudinally the stability of anhedonia in UHR individuals after 1-year follow-up period; and (c) to explore any significant correlation of anhedonia with psychopathology and functioning in the UHR subgroup both at baseline and after 12 months of follow-up.

SUBJECTS AND METHODS

Participants

All the participants (n=310) were young help-seekers recruited through the "Reggio Emilia At-Risk Mental States" (ReARMS) project between September 2012 and December 2017. ReARMS is a dedicated infrastructure for early intervention in psychosis implemented within all of adult and child/adolescent mental health services of the Reggio Emilia Department of Mental Health, a semi-urban catchment area of approximately 550.000 inhabitants, in the northern Italy (Pelizza et al. 2020a).

For the purpose of this study, inclusion criteria were: (a) specialist help-seeking; (b) age between 13 and 35 years; (c) presence of UHR status as defined by the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al. 2005), or (d) Duration of Untreated Psychosis (DUP) < 2 years in case CAARMS-FEP criteria (Yung et al. 2005) was detected at the initial assessment. In details, the CAARMS defines the following three diagnostic subcriteria and one or more need to be fulfilled for considering an individual at UHR of developing psychosis: (a) Genetic Risk and Functioning Deterioration (GRFD) syndrome: schizotypal personality disorder in the subject or history of psychosis in a first-degree relative combined with 30% drop in functioning for ≤ 1 month or chronic low functioning, as measured by the Social and Occupational Functioning Assessment Scale (SOFAS) (Yung et al. 2005) (the decline in functioning was estimated by subtracting the actual SOFAS score from the highest SOFAS score in the past year); (b) Attenuated Psychotic Symptoms (APS): sub-threshold positive psychotic symptoms within the past 12 months; and (c) Brief Limited Intermittent Psychotic Symptoms (BLIPS): criteria for psychosis met for < 7 day and remitting spontaneously (i.e. without anti-psychotic medication). Moreover, according to the CAARMS (Yung et al. 2005), FEP criteria are defined by operationalized clear-cut levels of fully (positive) psychotic symptoms occurring for at least 1 week, either on a daily basis or more than 3 times a week, with each symptom continuing for more than 1 hour on each occasion.

Exclusion criteria were: (a) history of affective and non-affective psychosis, according to the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revised (DSM-IV-TR) (APA 2000); (b) history of previous exposure to antipsychotics; (c) current substance dependence; (d) known intellectual disability (i.e. Intelligence Quotient < 70); and (e) neurological disorders, head injury or any other medical condition associated with psychiatric symptoms. In the present study, we considered previous exposure to antipsychotic (i.e. before ReARMS enrollment) as an equivalent of past psychotic episode. Indeed, according to the CAARMS (Yung et al. 2005), the psychosis threshold is essentially that at which antipsychotic medication would probably be commenced in common clinical practice.

All help-seekers entering the ReARMS protocol (and their parents, if minors) agreed to participate to the research and gave their written informed consent. Local relevant ethical approvals were sought for the study. Participant anonymity has been preserved. The current research has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experimental including humans.

Instruments

The psychopathological assessment for this study included the CAARMS[5], the Beck Depression Inventory-II (BDI-II) (Beck et al. 2006), the Schizotypal

Personality Questionnaire – Brief version (SPQ-B) (Raine & Benishay 1995), the Brief version of the Oxford-Liverpool Inventory of Feelings and Experiences (Brief-O-LIFE [BOL]) (Mason et al. 2005), and the World Health Organization Quality Of Life, Brief version (WHOQOL-BREF) (WHOQOL group 1996).

CAARMS

The CAARMS is a semi-structured clinical interview designed to cover different aspects of attenuated psychopathology, as well as functioning (via the integrated SOFAS module) (Yung et al. 2005). It takes approximately 1-1.5 hours to be administered and consists of 27 items that can be clustered in seven subscales: (a) "Positive Symptoms", (b) "Cognitive Change, Attention and Concentration", (c) "Emotional Disturbance", (d) "Negative Symptoms", (e) "Behavioral Change", (f) "Motor/Physical Changes", and (g) "General Psychopathology" (for details, see also supplementary materials ["Instruments" section]). In the present study, we used the approved Italian version of the CAARMS (CAARMS-ITA) (Raballo et al. 2013), which showed good to excellent inter-rater reliability (Pelizza et al. 2020b).

BDI-II

The BDI-II (Beck et al. 2006) is a widely used self-report questionnaire designed to measure the presence and the severity of depression in individuals aged 13-80 years. It contains 21 items, usually summed to provide a single total score. However, the BDI-II can be separated into two subscales reflecting the two main structural components of depression (i.e. "Cognitive" and "Somatic-Affective" subscale) (for details, see also supplementary materials ["Instruments" section]). In this study, we used the approved Italian adaptation of the BDI-II, which showed good psychometric properties in Italian clinical and non-clinical samples (Pelizza et al. 2020c).

SPQ-B

The SPQ-B is a brief (2-minute) 22-item self-report screener for the Schizotypal Personality Disorder (SPD). It contains a total score and three subscales to assess the three main SPD dimensions (i.e. "Cognitive-Perceptual Deficits", "Interpersonal Deficits, and "Disorganization") (for details, see also supplementary materials ["Instrument" section]). This questionnaire is recommended prior to a confirmatory clinical interview (Raine & Benishay 1995). However, its scores correlated significantly with independent clinical ratings of DSM-IV-TR schizotypal personality traits, indicating good to excellent criterion validity (Fonseca-Pedrero et al. 2014). In this research, we used an Italian translation adapted from the original English version (Raballo 2005), which showed good psychometric properties in Italian populations with early psychosis (Pelizza et al. 2020d).

BOL

The BOL is a 43-item self-report instrument designed to measure psychosis-like symptoms, which are supposed to be a likely expression of schizotypal personality traits (Cella et al. 2013). This true/false questionnaire includes four main subscales: "Unusual Experiences", "Cognitive Disorganization", "Introvertive Anhedonia", and "Impulsive Nonconformity" (for details, see also supplementary materials ["Instruments" section]). Reliability and validity of the BOL have been established in several experimental and clinical studies (Mason et al. 2005). In this research, we used the approved Italian adaptation of the BOL (Cella et al. 2013), which showed good reliability and validity in Italian UHR clinical samples (Pelizza et al. 2020e)

WHOQOL-BREF

The WHOQOL-BREF is an abbreviated 26-item version of the WHOQOL-100 assessment (WHOQOL group 1994), exploring different aspects of self-perceived quality of life. This self-report questionnaire is currently divided into four domains: (a) "Physical Health", (b) "Psychological Health", (c) "Social Relationships", and (d) "Environmental Health" (for details, see also supplementary materials ["Instruments" section]). In the present study, we used the Italian version of the WHOQOL-BREF, which showed good psychometric properties in Italian clinical populations (De Girolamo et al. 2000).

Anhedonia measures

For the purpose of the study, we adopted two different indexes of anhedonia, based on the CAARMS and the BOL. The CAARMS "Anhedonia" item 4.3 is a 7-point component capturing a lack of pleasure/interest and the withdrawal from all usual pleasant activities (for details, see also supplementary materials ["Instruments" section]). A score of ≥ 2 corresponds at least to a slight decline in pleasure experiences (Yung et al. 2005). More realistically, this item measures state-anhedonia aspects that could change over 12 months, also due to specific interventions or changes in the clinical status.

The BOL "Introvertive Anhedonia" subscale includes 10 true/false items that describe a lack of enjoyment from social and physical sources of pleasure, as well as avoidance of intimacy (Mason et al. 2005) (for details, see also supplementary materials ["Instruments" section]). A total score was calculated by summing all the ten anhedonic item subscores. This subscale was developed to measure specific trait features of the negative dimension of schizotypy (Cella et al. 2013).

Procedures

All the participants underwent an extensive diagnostic assessment (Pelizza et al. 2020a). The axis-I diagnosis was made according to DSM-IV-TR criteria by two trained ReARMS team members, using the

Structured Clinical Interview for DSM-IV-TR axis I Disorders (SCID-I) (First et al. 2002). After CAARMS interviews, participants were divided into three groups according to UHR/psychosis criteria: (a) UHR+ group (i.e. APS, BLIPS and GRFD), (b) FEP group, and (c) UHR- group (i.e. those individuals under the threshold of the CAARMS inclusion criteria) (Yung et al. 2005).

All the UHR/FEP help-seekers referred to the ReARMS protocol were assigned to a multi-professional team including a psychiatrist, a clinical psychologist and a case-manager for early rehabilitation, generally within 2-3 weeks. According to their symptoms, FEP and UHR individuals were then provided with a comprehensive two-year intervention package including (a) a multi-element psychosocial intervention (combining individual Cognitive-Behavioral Therapy [CBT], psychoeducational sessions for family members, and a recovery-oriented case management) and (b) a pharmacological treatment, according to current guidelines (Schmidt et al. 2015). The prescription of antipsychotics was avoided unless UHR subject (a) had an imminent risk of suicide or severe violence, (b) was overwhelmed by abruptly worsening full-blown psychotic symptoms, (c) was rapidly deteriorating in daily functioning, or (d) did not respond to any other treatment. Low-dose atypical antipsychotics were used. Selective serotonin reuptake inhibitor or benzodiazepines were used to treat depressive symptoms, anxiety, and insomnia.

In our adolescent and young adult help-seekers, socio-demographic characteristics and anhedonia levels (i.e. CAARMS item 4.3 and BOL "Introvertive Anhedonia" subscale scores at baseline) were examined by evaluating inter-group comparisons (i.e. FEP, UHR+, and UHR-). Moreover, within the UHR+ group, both at baseline and after 1 year of follow-up, we explored any significant correlation of anhedonia with functioning, psychopathology (i.e. positive, negative, disorganized, and depressive symptoms), quality of life, and schizotypal personality dimensions. Finally, we longitudinally monitored the stability of anhedonia measures in the UHR+ individuals along 1-year follow-up period.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS) for Windows, version 15.0 (SPSS Inc. 2010). All tests were two-tailed, with α=0.05. Non-parametric statistics were used, due to non-normality (Kolmogorov-Smirnov test, with Lilliefors significance correction, $p<0.05$) in all explorations.

Categorical data in intergroup comparisons were analyzed with Chi-square or Fisher's exact test, where appropriate (i.e. when any expected frequency was < 1 or 20% of expected frequency was ≤ 5). The Kruskal-Wallis and/or the Mann-Whitney U test (as post-hoc procedure with Holm-Bonferroni correction for multiple comparisons) (Holm 1979) were used to compare ordinal variables. Spearman's rho (ρ) correlation coefficients were used to examine between-variable associations. We also used Holm-Bonferroni correction to revise p-value for Spearman's correlation analysis (Holm 1979). Finally, in the UHR+ subgroup, the Wilcoxon test for repeated measures was used to examine the stability of anhedonia scores across 1-year follow-up period.

RESULTS

Over the course of the study, 310 adolescents (174 males (56.1%); mean age 21.25±5.84 years) consecutively entered the ReARMS protocol. Socio-demographic and clinical characteristics are reported in the Table 1.

Table 1. Demographic characteristics and anhedonia levels of the total sample and the three subgroups

Variable	Total sample (n=310)	UHR- (n=95)	UHR+ (n=78)	FEP (n=137)	χ^2	Post hoc test
Gender (males)	174 (56.1%)	45 (47.4%)	35 (44.9%)	94 (68.6%)	15.65[b]	FEP>UHR+=UHR-
Ethnic group (Caucasian)	267 (86.4%)	80 (84.2%)	68 (87.2%)	119 (86.9%)	0.43	-
Mother tongue (Italian)	278 (89.7%)	89 (93.7%)	69 (88.5%)	120 (87.6%)	2.42	-
Age	21.25±5.84	20.64±6.28	18.59±4.40	23.22±5.77	37.46[a]	FEP>UHR+=UHR-
Education (in years)	11.52±2.40	11.48±2.39	11.19±2.34	11.74±2.45	2.44	-
DUI (in weeks)	81.65±59.26	72.98±57.87	73.06±48.51	94.73±65.42	4.00	-
Comorbid substance abuse	103 (33.3%)	24 (25.3%)	14 (17.9%)	65 (47.4%)	23.41[a]	FEP>UHR+=UHR-
Anhedonia						
CAARMS item 4.3 subscore	2.90±1.87	1.76±1.77	3.38±1.48	3.46±1.78	51.58[a]	FEP=UHR+>UHR-
BOL "Introvertive Anhedonia" subscore	4.21±2.02	3.37±2.13	4.73±1.99	4.38±1.84	16.51[a]	FEP=UHR+>UHR-

Legend - Frequencies (percentages), mean ± standard deviation, Kruskal-Wallis and Chi-squared test (χ^2) values are reported. Post-hoc analyses were performed using the Mann-Whitney U test.
[a]$p<0.001$; [b]$p<0.01$; CAARMS = Comprehensive Assessment of At-Risk Mental States; FEP = First Episode Psychosis;
UHR+ = participants who met CAARMS Ultra-High Risk (UHR) criteria; UHR- = participants who were below CAARMS-defined UHR/FEP criteria;
DUI = Duration of Untreated Illness; BOL = Brief O-LIFE (Brief version of the Oxford-Liverpool Inventory of Feelings and Experiences)

Among the UHR+ group (n=78; 25.2% of the total sample), 71 met APS criteria (91% of UHR+ individuals), 4 met GRFD criteria, and 3 met BLIPS criteria.

The FEP group (n=137; 44.2% of the total sample) consisted of patients with DSM-IV-TR schizophrenia (n = 64; 46.7% of FEP individuals), affective (bipolar or major depressive) psychosis (n=29), psychotic disorder not otherwise specified (n=27), and brief psychotic disorder (n=17).

The remaining 95 participants (30.6% of the total sample) were below the CAARMS threshold for being considered at risk for psychosis and composed the UHR- group. They were diagnosed with DSM-IV-TR depressive disorders (n=37; 38.9% of UHR- individuals), non-schizotypal personality disorder (n=30), and anxiety disorders (n=28).

In comparison with UHR+ and UHR-, FEP patients showed a significantly higher age at ReARMS enrollment, as well as greater percentages of males and comorbid substance abuse at entry. No inter-group difference in terms of ethnic group, mother tongue, years of education, and Duration of Untreated Illness (DUI, meant as the interval [in weeks] between the onset of a prominent psychiatric symptom and the administration of the first pharmacological/psychological treatment) (Rapp et al. 2017) was found. However, within the total FEP subgroup, no significant association of anhedonia with gender, age, and comorbid substance abuse at baseline was observed (for details, see also supplementary materials [Table S1]).

Anhedonia in UHR+ individuals

At baseline, FEP and UHR+ individuals showed significantly higher CAARMS "Anhedonia" item 4.3 scores than UHR- peers (Table 1). Interestingly, no difference in CAARMS item 4.3 subscores was found UHR+ and FEP groups.

Compared to UHR-, UHR+ and FEP participants also had significantly higher BOL "Introvertive Anhedonia" subscale scores (Table 1). No difference in BOL anhedonia subscores was found between UHR+ and FEP samples.

At baseline, 39 (50%) UHR+ participants were taking antipsychotic medications (equivalent dose of chlorpromazine = 175.83±120.36 mg/day): of them, 35 (89.7%) UHR+ individuals used low-dose atypical antipsychotics (especially, risperidone and olanzapine).

As of December 2017, 22 UHR+ participants had a follow-up period of < 1 year and did not achieve the 12-month follow-up assessment time. Twenty-three (41.1%) out of the 56 UHR+ subjects who completed the 1-year follow-up period, were still taking antipsychotic medications (equivalent dose of chlorpromazine = 197.29 ± 167.13 mg/day).

With respect to the stability of anhedonia levels in the UHR+ subsample, while no significant difference was found between BOL "Introvertive Anhedonia" subscale scores at baseline and after 12-month follow-up period, a statistically significant decrease in severity of CAARMS item 4.3 subscore after 1 year of follow-up was observed (Table 2).

Within the total UHR+ group at baseline, CAARMS "Anhedonia" item 4.3 subscore showed significant positive correlations with CAARMS "Emotional Disturbance", "Negative Symptoms", "Behavioral Change", and "Motor-Physical Changes" dimension scores (in particular with CAARMS "Subjective Emotional Disturbance", "Observed Blunted Affect", "Alogia", "Avolition/Apathy", and "Impaired Role Functioning" item subscores), as well as with CAARMS "Depression" item subscore (Table 3). Even excluding CAARMS "Anhedonia" item 4.3 from "Negative Symptoms" dimension score, Spearman's correlation coefficient remained significant. Moreover, CAARMS anhedonia levels also had significant positive correlations with BDI-II total score, BDI-II "Cognitive" and "Somatic-Affective" subscale scores, and BDI-II item 9 ("Suicidal Ideation") subscore. Interestingly, CAARMS "Anhedonia" item 4.3 score showed no significant correlation with CAARMS "Positive Symptoms" and "Cognitive Change" subscores, as well as with WHOQOL and SPQ-B scores.

Differently, within the UHR+ total sample at baseline, BOL "Introvertive Anhedonia" subscale score had significant negative correlations with all the WHOQOL subscale scores, as well as significant positive correlations with SPQ-B total score and SPQ-B "Interpersonal Deficits" and "Disorganization" dimension subscores (Table 3). Moreover, BOL anhedonia levels showed no correlations with the other psychopathological parameters, with the exception of significant positive associations with BDI "Cognitive" subscale and BDI item 9 ("Suicidal Ideation") scores. As expected, no correlation between CAARMS "Anhedonia" item 4.3 and BOL "Introvertive Anhedonia" subscale scores was found.

Table 2. Anhedonia levels along 1-year follow-up period in the UHR+ group (n=56)

Anhedonia	Baseline (T0)	1-year (T1) follow-up assessment	Z
CAARMS item 4.3 subscore	3.38±1.48	2.32±1.94	-4.18[a]
BOL "Introvertive Anhedonia" subscale score	4.73±1.99	4.66±2.04	-0.92

Legend - CAARMS = Comprehensive Assessment of At-Risk Mental States; UHR+ = individuals who met CAARMS Ultra-High Risk (UHR) criteria; BOL = Brief-O-Life (Brief version of the Oxford-Liverpool Inventory of Feelings and Experiences); T0 = anhedonia score at baseline; T1 = anhedonia score after 1-year follow-up period; mean ± standard deviation and Wilcoxon test (Z) values are reported; [a]$p < 0.001$.

Table 3. Spearman's correlations between anhedonia levels and other psychopathological features in the UHR+ group (n=78)

Psychopathological variables	CAARMS item 4.3 (ρ)	BOL "Introvertive Anhedonia" subscale (ρ)
SOFAS	-0.298	0.139
CAARMS		
Positive Symptoms	0.062	0.252
Unusual thought content	0.121	0.076
Non bizarre ideas	-0.048	0.128
Perceptual abnormalities	-0.023	0.122
Disorganized speech	0.133	0.159
Cognitive change	0.106	0.114
Subjective cognitive change	0.204	-0.045
Observed cognitive change	0.034	0.148
Emotional disturbance	0.423[a]	0.073
Subjective emotional disturbance	0.408[a]	-0.056
Observed blunted affect	0.413[a]	0.089
Observed inappropriate affect	-0.026	0.175
Negative Symptoms (without item 4.3)	0.591[a]	-0.020
Alogia	0.352[b]	-0.017
Avolition/apathy	0.617[a]	-0.035
Behavioral change	0.411[a]	0.043
Social isolation	0.311	0.021
Impaired role functioning	0.469[a]	0.076
Disorganizing/odd/stigmatizing behavior	0.089	-0.091
Aggressive/dangerous behavior	0.158	0.101
Motor/physical change	0.366[b]	0.090
Subjective impaired motor functioning	0.327	-0.045
Objective impaired motor functioning	0.274	0.176
Subjective impaired bodily sensation	0.267	0.131
Subjective impaired autonomic functioning	0.143	-0.032
General psychopathology	0.216	0.126
Mania	-0.135	-0.150
Depression	0.388[a]	0.076
Suicidality/self-harm	0.138	0.022
Mood swings/lability	0.115	0.028
Anxiety	0.294	0.131
Obsessive-compulsive symptoms	0.196	0.003
Dissociative symptoms	-0.027	0.198
Subjective impaired tolerance to normal stress	0.268	0.044
BDI-II		
Total score	0.374[c]	0.293
Cognitive subscale	0.388[c]	0.524[a]
Somatic-Affective subscale	0.338[c]	0.195
Item 9 ("Suicidal ideation") score	0.321[c]	0.468[c]
WHOQOL-BREF		
Physical health	-0.213	-0.380[c]
Psychological health	-0.195	-0.380[c]
Social relationships	-0.106	-0.463[a]
Environmental health	-0.099	-0.397[b]
SPQ-B		
Total score	-0.090	0.432[a]
Cognitive-Perceptual deficits	-0.199	0.201
Interpersonal deficits	0.061	0.472[a]
Disorganization	0.067	0.353[b]

Legend: CAARMS = Comprehensive Assessment of At-Risk Mental States; UHR+ = participants who met CAARMS Ultra-High Risk (UHR) criteria; BOL = Brief-O-LIFE (Brief version of the Oxford-Liverpool Inventory of Feelings and Experiences); SOFAS = Social and Occupational Functioning Assessment Scale; BDI-II = Beck Depression Inventory-II edition; WHOQOL-BREF = World Health Organization Quality Of Life-Brief version; SPQ-B = Schizotypal Personality Questionnaire – Brief version; Holm-Bonferroni corrected p-value: [a]$p<0.001$, [b]$p<0.01$, and [c]$p<0.05$. Spearman's correlation coefficient (ρ) values are reported.

Table 4. Spearman's correlations between anhedonia levels and other psychopathological features after 1 year of follow-up in the UHR+ group (n=56)

Psychopathological variables	CAARMS item 4.3 (ρ)	BOL "Introvertive Anhedonia" subscale (ρ)
SOFAS	-0.781[a]	-0.058
CAARMS		
Positive Symptoms	0.718[a]	0.174
Unusual thought content	0.655[a]	0.220
Non bizarre ideas	0.614[a]	0.006
Perceptual abnormalities	0.525[a]	0.179
Disorganized speech	0.459[a]	0.308
Cognitive change	0.473[a]	0.078
Subjective cognitive change	0.516[a]	0.056
Observed cognitive change	0.275	0.150
Emotional disturbance	0.576[a]	0.175
Subjective emotional disturbance	0.580[a]	0.132
Observed blunted affect	0.425[c]	0.177
Observed inappropriate affect	0.216	0.225
Negative Symptoms (without item 4.3)	0.807[a]	0.132
Alogia	0.488[a]	0.191
Avolition/apathy	0.873[a]	0.092
Behavioral change	0.736[a]	0.144
Social isolation	0.713[a]	0.222
Impaired role functioning	0.800[a]	0.104
Disorganizing/odd/stigmatizing behavior	0.344	0.113
Aggressive/dangerous behavior	0.276	-0.083
Motor/physical change	0.396[a]	0.066
Subjective impaired motor functioning	0.269	-0.023
Objective impaired motor functioning	0.244	0.167
Subjective impaired bodily sensation	0.353	0.069
Subjective impaired autonomic functioning	0.311	-0.005
General psychopathology	0.660[a]	0.154
Mania	-0.019	-0.283
Depression	0.689[a]	0.210
Suicidality/self-harm	0.363	0.060
Mood swings/lability	0.297	0.064
Anxiety	0.537[a]	0.221
Obsessive-compulsive symptoms	0.327	0.173
Dissociative symptoms	0.208	0.096
Subjective impaired tolerance to normal stress	0.461[a]	0.141
BDI-II		
Total score	0.693[a]	0.559[b]
Cognitive subscale	0.747[a]	0.474[c]
Somatic-Affective subscale	0.645[a]	0.571[b]
Item 9 ("Suicidal ideation") score	0.509[c]	0.508[b]
WHOQOL-BREF		
Physical health	-0.671[a]	-0.476[b]
Psychological health	-0.697[a]	-0.309[c]
Social relationships	-0.677[a]	-0.370[c]
Environmental health	-0.685[a]	-0.360[c]
SPQ-B		
Total score	0.337	0.426[b]
Cognitive-Perceptual deficits	0.226	0.243
Interpersonal deficits	0.328	0.479[a]
Disorganization	0.381	0.382[c]

Legend – CAARMS = Comprehensive Assessment of At-Risk Mental States; UHR+ = participants who met CAARMS Ultra-High Risk (UHR) criteria; BOL = Brief-O-LIFE (Brief version of the Oxford-Liverpool Inventory of Feelings and Experiences); SOFAS = Social and Occupational Functioning Assessment Scale; BDI-II = Beck Depression Inventory-II edition; WHOQOL-BREF = World Health Organization Quality Of Life-Brief version; SPQ-B = Schizotypal Personality Questionnaire – Brief version; Holm-Bonferroni corrected p-value: [a]$p < 0.001$, [b]$p < 0.01$, and [c]$p < 0.05$. Spearman's correlation coefficient (ρ) values are reported.

After 1 year of follow-up, CAARMS "Anhedonia" item 4.3 subscore showed significant positive correlations with all CAARMS dimension scores (in particular, with CAARMS "Unusual Thought Content", "Non Bizarre Ideas", "Perceptual Abnormalities", "Disorganized Speech", "Subjective Cognitive Change", "Subjective Emotional Disturbance", "Observed Blunted Affect", "Alogia", "Avolition/Apathy", "Social Isolation", "Impaired Role Functioning", "Depression", "Anxiety", and "Subjective Impaired Tolerance to Normal Stress" item subscores), as well as with all BDI-II scores (including BDI-II "Suicidal Ideation" item 9 subscore) (Table 3). Moreover, at 1-year follow-up assessment, CAARMS anhedonia had significant negative correlations with SOFAS and all WHOQOL-BREF domain scores.

Otherwise, after the 1 year of follow-up, BOL "Introvertive Anhedonia" subscale score showed positive correlations with all BDI-II scores, as well as with SPQ-B total score and SPQ-B "Interpersonal Deficits" and "Disorganization" dimension subscores (Table 3). Furthermore, BOL anhedonia had negative correlations with all WHOQOL-BREF domain scores.

DISCUSSION

First aim of the current study was to assess anhedonia levels in young people at UHR of psychosis compared to non-UHR and FEP peers. At baseline, UHR+ individuals had higher levels of anhedonia (as measured both on the BOL "Introvertive Anhedonia" subscale and on the CAARMS item 4.3 scores) than UHR- subjects. This is in line with results previously reported by Cressman et al. (2015) and Jhung et al. (2016) in two UHR+ samples compared to healthy controls using Chapman's anhedonia scales.

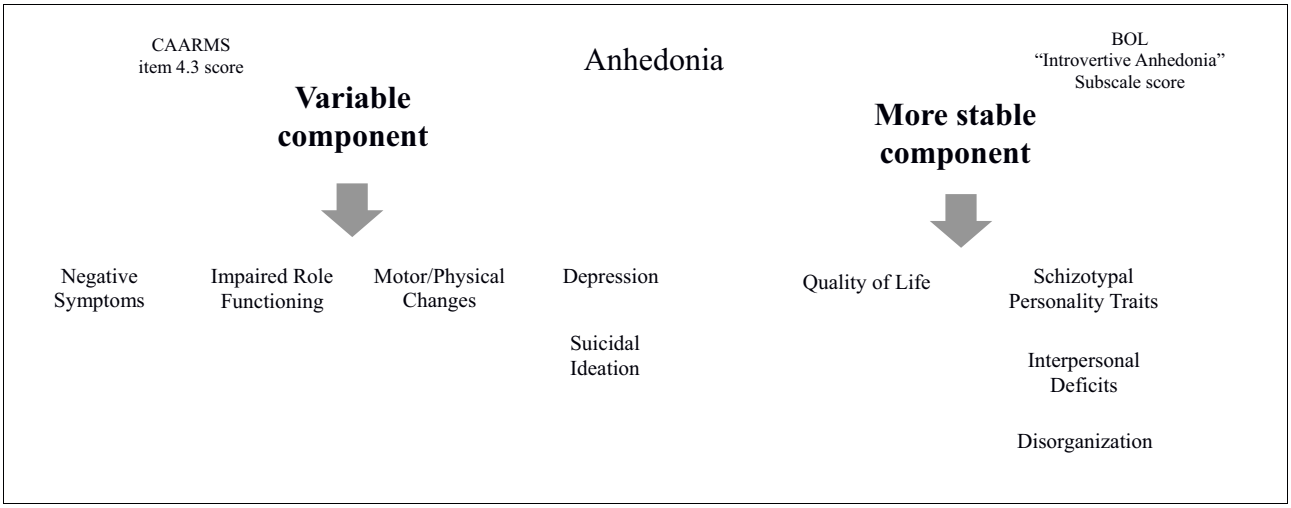
However, in the present research no difference in BOL and CAARMS anhedonia scores was observed between FEP and UHR+ groups. This is not in agreement with another study (Jhung et al. 2016) reporting higher levels of current and noncurrent anhedonia in 24 young individuals at UHR of psychosis (age = 19.9 ± 3.6 years; 54.2%) compared to 25 patients with recent-onset schizophrenia (age = 21.9±4.7 years; 40% males), independently from comorbid depression. Overall, these findings suggest that there is a significant impairment in the ability to feel pleasure and to be engaged in rewarding/pleasant activities already during the prodromal phase of psychosis. Moreover, anhedonia in UHR+ subjects appears to be indistinguishable in severity from that of FEP patients, even at their first help-seeking contact with mental health services.

In the present research, while we observed stability in BOL "Introvertive Anhedonia" subscale scores after 1-year follow-up period in UHR+ individuals, a significant reduction in severity of CAARMS anhedonia subscore was found. As expected, together with evidence of no correlation between CAARMS and BOL anhedonia scores in our young UHR+ participants, these findings seem to suggest the presence of two different temporal characteristics in the inability to experience pleasure: (a) a variable, state-like component (state anhedonia?) that could change over time reflecting fluctuations in the clinical status, and (b) a more stable, trait-like component (trait anhedonia?) that could reflect specific aspects of the negative dimension of schizotypy (Cella et al. 2013). However, when interpreting these results, a major issue to be underline is the fact that the two anhedonia measures (i.e. BOL "Introvertive Anhedonia" subscale score and CAARMS item 4.3 subscore) are unbalanced, with one measure being a sum of 10 items and the other one being a single question.

Furthermore, at baseline we found two different correlation patterns. BOL anhedonia in UHR+ participants showed significant correlations with specific dimensions of schizotypy (i.e. disorganization and interpersonal deficits), as well as with an impairment in self-perceived quality of life. Differently, positive associations were found between CAARMS anhedonia and the following four psychopathological features: (1) negative symptoms (including emotional disturbances), (2) impaired role functioning (3) motor/physical changes, and (4) depression (as measured both on self-reports and clinical interview) (Figure 1). However, in our UHR+ participants, clinical depression exclusively rated on BDI-II self-report questionnaire was also correlated with BOL anhedonia. Therefore, according to Blanchard et al. (2001), even presumed trait measures of anhedonia can covary with current symptom status and change substantially over time.

In line with what reported in comparable UHR studies (Cressman et al. 2015; Strauss et al. 2018), our findings confirm that UHR+ individuals have anhedonic features that are significantly related to the severity of their negative symptoms and to their role functioning impairment. This pattern suggests that anhedonia could represent an early clinical feature of risk for psychosis (Cressman et al. 2015; Pelizza et al. 2018) specifically affecting role functioning. This is also concordant with the finding of a correlation of genetic risk for schizophrenia (in terms of schizophrenia polygenic risk score) with early negative symptoms rather than positive symptoms in adolescence (Jones et al. 2016).

Consistently with what reported in previous studies on UHR+ individuals (Gruber et al. 2018; Strauss et al. 2018), our findings confirm a significant association of baseline anhedonia with concurrent depression (including suicidal ideation) (Figure 1). Together with evidence of a high prevalence (approximately 48%) of DSM-IV-TR depressive disorders in our UHR+ participants (for details, see also supplementary materials [Table S2]), these results support the hypothesis of anhedonia as a clinical risk factor for the development of depressive symptoms more generally, in addition to psychotic symptoms specifically (Radua et al. 2018). Both CAARMS and BOL anhedonic characteristics seem



Legend - CAARMS = Comprehensive Assessment of At-Risk Mental States;
BOL = Brief-O-LIFE (Brief version of the Oxford-Liverpool Inventory of Feelings and Experiences)

Figure 1. Baseline anhedonia in young people with a psychosis risk syndrome: psychopathological hypotheses

to be involved in this comorbidity. Moreover, in line with what reported by Ducasse et al. (2018) in a meta-analysis on adults with major depressive disorder, in the current research both baseline CAARMS and BOL anhedonia also showed a significant association with suicidal ideation in the UHR+ subgroup. These findings suggest that UHR+ individuals with anhedonic features may be not only at risk of psychosis, but also at risk of suicide.

Finally, within the total UHR+ sample, at baseline we found significant correlations between CAARMS anhedonia and CAARMS motor/physical and emotional changes including in Huber's Basic Symptoms (BS) (Yung et al. 2005). BS are subtle, subjective experienced disturbances in mental processes (including thinking, speech, attention, perception, affect, stress tolerance, and drive) that are considered as an immediate symptomatic expression of the neurobiological substrate underlying psychosis (specifically schizophrenia) (Schultze-Lutter & Theodoridou 2017). Overt and attenuated psychotic symptoms are assumed to develop later as a result of poor coping with BS and/or stressors when an individual's protective mechanisms are overstrained (Maggini et al. 2003). In line with results previously reported by Pelizza & Ferrari (2009), our findings further support a potential role of the inability to feel pleasure as an early emotional self-disturbance that subjectively marks the prodromal phase of psychosis and that is specifically related to an altered sense of agency involving motor/physical disturbances (such as subjective experience of dys-coordination, motor lags and/or bradykinesia). In this regards, recent neuroscientific research in the framework of psychosis risk syndrome confers plausibility to the hypothesis of motor impairment as a direct manifestation of a latent pathophysiological mechanism causally involved in the neurodevelopment of psychotic risk, especially in schizophrenia spectrum disorders (Poletti et al. 2018). At a neurophysiological level, anhedonia and impairments in specific motor circuits (such as corollary discharge and/or sensorimotor integration) that seem to underpin psychotic experiences, could share the same neurobiological systems (e.g., alterations of dopamine levels both in basal ganglia and cortical-mesolimbic projections) (Poletti et al. 2017).

Differently from previous studies (Cressman et al. 2015, Jhung et al. 2016), in the present research baseline anhedonia levels in UHR+ individuals are independent from positive symptoms. In this regards, our findings is consistent with results of studies on patients with schizophrenia (Pelizza & Ferrari 2009, Pelizza et al. 2012).

After 1 year of follow-up, CAARMS anhedonia showed a broader spectrum of association with functioning, psychopathology, and quality of life. In details, the variable (state-like) component of the inability to feel pleasure seems to have a more enduring connection with negative symptoms (including emotional disturbance), depression (including suicidal ideation), impaired role functioning, and motor/physical changes, and a more dynamic relation with poorer quality of life and other specific psychopathological aspects experienced by UHR+ people (i.e. cognitive change, positive symptoms, anxiety, and social isolation). Overall, these findings suggest that in young subjects at UHR of psychosis, enduring levels of anhedonia could be considered as a clinical indicator of greater psychopathological severity, a bad role and social functioning, and a worse quality of life.

Differently, after 12 months of follow-up, BOL anhedonia maintained a stable connection with a poorer quality of life and those schizotypal personality aspects concerning interpersonal deficits and disorganization. However, BOL "Introvertive Anhedonia" subscale also seems to have a temporal dynamic association with comorbid depression.

In this regards, Azis et al. (2018) reported that social anhedonia was included in one ("Emotion") of the two negative symptom dimension isolated by an exploratory factor analysis in a sample of 214 young people at UHR of psychosis, which resulted to be associated with a poorer social functioning. Furthermore, in a 1-year longitudinal study examining negative symptoms in 138 UHR+ individuals, Piskulic et al. (2012) observed that social anhedonia remained in a moderate severity range for 54% of participants, and that it was more severe and persistent over time in those who converted to psychosis.

Limitations

This research has some methodological limitations. First, differences in anhedonia levels at the follow-up time-point between BOL and CAARMS measures might be influenced by the fact that BOL "Introvertive Anhedonia" subscale score is more stable, being computed as a sum of 10 items. Differently, CAARMS item 4.3 subscore is just a single question, whose answer is probably more instable. Therefore, this possible statistical artefact must be taken into consideration when interpreting results and it still remains a point of criticism.

Likewise, the findings of significant correlations could be derived from the difference of rater-assessment scales form subjective self-reports: i.e. correlations of trait anhedonia (self-report) were mainly found with self-reports of WHOQOL and schizotypy, while associations of state anhedonia (rater-assessed item) were found with CAARMS rater-assessed dimensions. Thus, the method of assessment could be more relevant than the state-trait distinction.

Moreover, differences in anhedonia levels could be also related to the fact that BOL questions focus more on internal experiences (i.e. what the participants prefer or like), while CAARMS item 4.3 seems to capture a broad lack of pleasure/interest and withdrawal/asociality. In particular, asociality does not coincide with how social anhedonia is currently conceptualized and defined (Pelizza et al. 2012, Cressman et al. 2015).

Second, data are mostly cross-sectional. Thus, the predictive power of anhedonia measures in determining quality of life, psychopathology, and functioning impairment cannot be correctly examined.

Third, our participants were not all antipsychotic-free UHR+ subjects. Indeed, antipsychotic and other psychotropic medications can have indirect or direct pathophysiological effects on mechanisms underlying hedonic response, creating a normalizing effect in individuals who are stably treated for many weeks (Strauss et al. 2018). However, in the present study no significant correlations between anhedonia measures and antipsychotic medications were found (for details, see also supplementary materials (Table S3)).

Fourth, in the current study the inability to feel pleasure was assessed as a subscale measure of 10 introvertive anhedonic aspects (i.e. BOL anhedonia subscale) or as a single item (i.e. CAARMS item 4.3). These instruments, not developed as stand-alone measures, may lack reliability and may provide a limited coverage of anhedonic characteristics (for example, physical aspects of pleasure are poorly assessed by these questionnaires). Therefore, future research would benefit from the use of dedicated, validated measures of anhedonia, such as the Chapman's Anhedonia scales (Chapman & Chapman 1978, Eckblad et al. 1982) or the Snaith-Hamilton Pleasure Scale (Snaith et al. 1995).

Finally, in the present research, we used a self-reported instrument (the BDI-II) for measuring depression severity. In order to increase the reliability and stability of the scores, clinician-rated scales for depression (such as the Calgary Depression Scale for Schizophrenia (CDSS), which showed good psychometric properties in UHR populations) (Rekhi et al. 2018) should also be used to confirm our promising findings.

CONCLUSIONS

Anhedonia is relevant in the psychosis risk syndrome and its severity is substantially indistinguishable from that of FEP patients. Moreover, the inability to experience pleasure in young subjects at UHR for psychosis is related to a worse quality of life and a more severe functioning deterioration, as well as higher levels of negative symptoms, depression, and suicidal ideation.

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Contribution of individual authors:

Lorenzo Pelizza & Andrea Raballo designed the study.

Silvia Azzali, Federica Paterlini, Sara Garlassi, Ilaria Scazza & Luigi Rocco Chiri collected data.

Lorenzo Pelizza, Michele Poletti, Simona Pupo & Andrea Raballo conducted the main data analysis.

Lorenzo Pelizza, Michele Poletti & Andrea Raballo drafted the manuscript.

All authors read and approved the final version of the manuscript.

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