Distinct profiles of anhedonia and reward processing and their prospective associations with quality of life among individuals with mood disorders

Alexis E. Whitton, Poornima Kumar, Michael T. Treadway, Ashleigh V. Rutherford, Manon L. Ironside, Dan Foti, Garrett Fitzmaurice, Fei Du and Diego A. Pizzagalli

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INTRODUCTION
Depression is the leading mental health contributor to the Global Burden of Disease and affects an estimated 300 million people worldwide [1]. Although timely intervention substantially improves prognosis [2], increased rates of treatment uptake have unfortunately not coincided with a reduction in depression-related disability [3]. Indeed, for a substantial proportion of individuals with depression, poor functioning and quality of life persist even after increased rates of treatment use. Here, we examined whether anhedonia—an often recalcitrant and impairing symptom of depression—along with its neural correlates, was associated with longitudinal changes in patient-reported quality of life among individuals seeking treatment for mood disorders. We recruited 112 participants, including n=80 individuals with mood disorders (58 unipolar, 22 bipolar) and n=32 healthy controls (63.4% female). We assessed anhedonia severity along with two electroencephalographic markers of neural reward responsiveness (scalp-level ‘Reward Positivity’ amplitude and source-localized reward-related activation in the dorsal anterior cingulate cortex), and assessed quality of life at baseline, 3- and 6-month follow-up. Anhedonia emerged as a robust correlate of quality of life cross-sectionally and longitudinally among individuals with mood disorders. Furthermore, increased neural reward responsiveness at baseline was associated with greater improvements in quality of life over time, and this improvement was mediated by longitudinal improvements in anhedonia severity. Finally, differences in quality of life observed between individuals with unipolar and bipolar mood disorders were mediated by differences in anhedonia severity. Our findings indicate that anhedonia and its reward-related neural correlates are linked to variability in quality of life over time in individuals with mood disorders. Treatments capable of improving anhedonia and normalizing brain reward function may be necessary for improving broader health outcomes for individuals seeking treatment for depression.

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which are not readily assessed by biological or clinician-rated measures of disease severity [9]. In the context of depression, PROMs can highlight which features of depression most strongly drive illness burden, and importantly, which features must be better targeted via treatment to improve health outcomes.

Anhedonia is increasingly recognized as a predictor of poorer outcomes and is an important factor contributing to depression-related disease burden [10]. Even after controlling for overall depression severity, more severe anhedonia predicts greater psychosocial impairment [5], increased suicidal ideation [11], greater psychiatric [12] and medical [13] comorbidity, and increased caregiver stress [14]. Anhedonia and its associated features (e.g., loss of motivation) are also a top treatment priority for healthcare providers and consumers due to their profound impact on self-care, daily routines, and interpersonal relationships [15]. This is worrying, given that anhedonia can be especially recalcitrant, responding poorly to pharmacological [16, 17], psychological [18], and neurostimulation therapy [19].
Understanding the mechanistic links between anhedonia and quality of life is crucial for identifying treatment targets that can improve outcomes for people with depression.

Anhedonia is linked to impairments in aspects of reward processing [10] subsumed under the Research Domain Criteria’s (RDoC) Positive Valence Systems (PVS; [20]). The PVS subdomain of reward learning has emerged as a promising candidate implicated in anhedonia pathophysiology given that it correlates with anhedonia severity cross-sectionally and prospectively [21, 22] and covaries with treatment-related improvements in anhedonia [23]. Although no studies have specifically examined links between reward learning and quality of life, findings from recent work provide preliminary evidence of a mechanistic link between activation within reward learning neurocircuitry and functional outcomes. Specifically, Eckstrand et al. [24] examined associations between neural reward prediction error signals, which are critical for reward learning [25], and changes in symptoms and functioning in individuals with psychological distress. Stronger reward prediction error signals predicted greater improvements in psychosocial functioning over six months, and this improvement was mediated by improvements in anhedonia [24]. These findings suggest that reward learning and the underlying neurocircuitry may be an important target for treatment.

Recently, we reported findings from a study that adopted an RDoC approach to examine whether three distinct aspects of reward learning neurocircuitry—striatal reward prediction error signals, anterior cingulate cortex (ACC) reward prediction error signals, and prefrontal glutamatergic neurotransmission—predicted longitudinal symptom trajectories in individuals with mood disorders [26]. Among the three reward learning markers examined, ACC reward prediction error signals, measured via the Reward Positivity (RewP) event-related potential (ERP) component, were associated with anhedonia severity. The RewP is a scalp-recorded ERP that occurs following reward feedback, and is thought to reflect reward-related signals in the ACC that have possible origins in the striatum [27, 28]. The RewP is blunted in individuals with acute [29] and remitted [30] depression, predicts depression onset [31], and is predictive of a range of depressive illness features associated with increased morbidity, including chronicity and recurrence [32], as well as suicidal ideation [33]. However, no study has examined whether the RewP is associated with anhedonia severity. The current study extends this prior work by examining whether the RewP is associated with anhedonia severity.

To address this knowledge gap, we examined whether RewP amplitude (scalp-level), RewP-related activation in the ACC (source localized), and anhedonia severity, were associated with quality of life cross-sectionally and longitudinally among individuals with mood disorders. In doing so, we were informed by the conceptual model of patient outcomes proposed by Wilson and Cleary [34], which posits that biological/physiological factors can be linked to subjective quality of life via specific symptoms and their impact on functioning in different life domains. Accordingly, we aimed to identify the extent to which these two neural markers of reward processing were linked to aspects of quality of life via their associations with anhedonia, and whether this association was specific to anhedonia as opposed to other mood-related symptoms. We hypothesized that individuals with mood-related pathology who showed more severe levels of anhedonia would show poorer quality of life cross-sectionally and longitudinally. Furthermore, given that blunted RewP amplitude has been linked to poorer prognosis [32, 33] and was associated with worse anhedonia in our prior study [26], we predicted that reduced RewP amplitude and RewP-related activation in ACC at baseline would predict poorer quality of life longitudinally.

MATERIALS AND METHODS

Study design

Data were collected as part of a broader longitudinal naturalistic study examining reward learning in individuals with mood disorders (n = 80) and controls (n = 32), which we have described previously [26]. Sample size was based on power calculations performed for the broader study. We used effect sizes observed in our preliminary work, which showed associations between reward learning metrics and anhedonia ranging from r = −0.41 to r = −0.59. Using these correlation sizes, a total of 80 individuals with mood disorders leads to a power of >0.97 to detect relations between reward learning metrics and to predict clinical outcome in a naturalistic follow-up study design, assuming 15% attrition. This broader study implemented a novel recruitment strategy wherein, rather than DSM diagnoses, participants were recruited based on their performance on a probabilistic reward task (PRT; [21]) that objectively assessed reward learning (see Supplementary Methods 1.1–1.2 for detail). This novel approach to recruitment meant that the full range of reward learning performance was represented within the mood disorders group, allowing us to assess how variability in reward learning and the underlying neurocircuitry was associated with variability in symptom trajectories, as reported in our prior paper [26]. Participants completed five study visits: 1) PRT screening and diagnostic assessment, 2) baseline EEG/ERP, 3) baseline MRI, 4) a 3-month follow-up assessment, and 5) a 6-month follow-up assessment.

In our prior paper, we found that the RewP was associated with anhedonia severity. The current study extends this prior work by examining whether the RewP is associated with individual differences in quality of life, and whether any association may be mediated by individual differences in anhedonia.

Participants

All participants seeking treatment for mood disorders (n = 80) were recruited through Massachusetts General Hospital and McLean Hospital, and healthy controls (n = 32) were recruited from the community. All participants were required to be fluent in English, have normal or corrected-to-normal vision, and be right-handed. Exclusionary criteria included: illicit drug use (indicated by a positive urine drug screen), history of seizure disorder, or a history of head injury or loss of consciousness. Inclusion criteria for the mood disorders group were: mood-related psychotic illness (depression, mixed episode, or hypomania) severe enough to cause distress impairment, as assessed via the Structured Clinical Interview for DSM-IV-TR [36]. Exclusion criteria for the mood disorders group were: electroconvulsive therapy in the past two years, psychosis or other exclusionary comorbidities (Supplementary Methods 1.3–1.4). Healthy controls were required to have no past or current use of psychotropic medication, no current or lifetime DSM-IV psychiatric disorder, no first degree relative with a known mood or psychotic disorder, and a Beck Depression Inventory-II [37] score less than 10. Controls were excluded if they had recently taken an exclusionary medication (Supplementary Methods 1.3). All procedures were approved by the McLean Hospital Institutional Review Board and all participants provided written informed consent after receiving a complete description of the study and prior to participating.

Measures of Quality of Life

Influenced by Wilson and Cleary’s Conceptual Model of Patient Outcomes [34], we examined two aspects of quality of life: (1) health-related quality of life, which captures perceptions of the impact an illness and its treatment has on quality of life, and (2) overall life enjoyment and satisfaction, which captures quality of life across multiple domains (not exclusively in the context of an illness).

Health-Related Quality of Life: The Short Form Health Survey (SF-36)

The SF-36 [38] is a 36-item self-report measure assessing health-related quality of life. Items assess eight domains: physical functioning, role limitations due to physical problems, bodily pain, perceived general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Items are added and converted to a scale from 0 (worst) to 100 (best). Domain scores were reduced to two general components assessing the impact of physical (PCS) and mental (MCS) health problems on quality of life, and were standardized using U.S. normative data [39].

Life Enjoyment and Satisfaction: Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q)

The Q-LES-Q [40] is a 16-item self-report scale assessing overall enjoyment and satisfaction in the domains of physical health, mood, work, household and leisure activities, social relationships, daily functioning, sexual interest,
economic status, vision, ability to get around physically, overall well-being, and medication. Items are rated from 1 (“very poor”) to 5 (“very good”), with higher scores indicating better enjoyment and satisfaction with life. The first 14 items were summed to create a total score (range: 14–70), which was expressed as a percentage of the maximum total score of the items completed (0–100). The normal range observed in community samples is 70–100 [40].

**Measures of symptom severity**

Mood and anxiety symptoms were assessed using the 62-item Mood and Anxiety Symptom Questionnaire [41], which allows dissociation of anhedonia from non-anhedonic symptoms of depression and anxiety. The measure includes four subscales that assess Anhedonic Depression (AD), Anxious Arousal (AA), General Distress due to Depression (GDD), and General Distress due to Anxiety (GDA).

**Measures of neural reward responsiveness**

In our broader study [26], we examined three neural reward learning markers as predictors of symptoms longitudinally (the broader methodology is described in the Supplementary Methods 1.5–1.6). For the current study, we focused on the link between quality of life and the RewP, given that in the broader study, the RewP was correlated with anhedonia severity. Specifically, we examined variation in RewP using two metrics – ΔRewP amplitude and ΔRewP-related dACC CSD:

**ΔRewP amplitude**

The RewP following receipt of monetary reward on correct rich and lean trials was computed from scalp-recorded EEG acquired while participants performed a counterbalanced version of the PRT. The EEG was recorded using a 128-channel Hydrocel Geodesic Sensor Net system (Electrical Geodesics, Inc.) and sampled at 250 Hz (bandwidth, 0.1–100 Hz; impedances < 100 kΩ). Following pre-processing, a temporospatial PCA was used to separate the RewP from overlapping ERP components (Supplementary Methods; Fig. S1). Analyses focused on the component most consistent with the RewP (TF8/SF2; Fig. 1). The difference in RewP amplitude following reward feedback on lean versus rich trials was then computed to yield our first metric of neural reward responsiveness (ΔRewP amplitude). The difference score was hypothesized to capture the degree to which reward prediction errors differ as a function of reward probability.

**ΔRewP-related dACC CSD**

Standardized low-resolution electromagnetic tomography (sLORETA) [42] was used to assess reward-related activation in brain regions thought to drive scalp-level RewP signals. The peak amplitude of the RewP PCA component on rich trials (occurring from 248–252 ms post-feedback) was extracted and sLORETA was used to regress this peak value on mean CSD across the whole brain from −20 ms to +20 ms around this peak on rich trials. This analysis revealed voxels where variation in RewP amplitude correlated with variations in CSD across the cortex. Images were thresholded at p < 0.005 uncorrected. Consistent with our hypothesis that the RewP reflects an ACC-mediated reward prediction error signal, results revealed a single cluster in Brodmann area 32 (corresponding to dACC; Fig. 1), where CSD was correlated with RewP amplitude. The mean CSD in this cluster was extracted for rich and lean trials, and a difference score computed to yield our second metric of reward responsiveness (ΔRewP-related dACC CSD).

**Statistical analysis**

**Bivariate associations.** Analyses were conducted using R version 4.2.1 in RStudio [43]. Pearson’s correlations were used to examine the bivariate associations between anhedonia, ΔRewP markers, and quality of life in those with mood disorders at baseline. These analyses were supplemented with repeated measures correlations, conducted using the rmcorr package [44], which assessed the common intrapersonal correlation between anhedonia and quality of life measures at the three assessment time points. Benjamini-Hochberg correction was used to correct for multiple correlations [45].

**Longitudinal associations**

**Model-building:** Hierarchical linear mixed effect modeling was used to examine the relationship between anhedonia severity, ΔRewP markers, and changes in quality of life in those with mood disorders over time. This was implemented using the lme4 package [46] and was conducted in two stages. In the first stage, we examined the association between anhedonia and quality of life using three models of increasing complexity. First, we considered a simple model that included as predictors Diagnosis (dummy-coded 0 = unipolar; 1 = bipolar), Time (entered as a continuous variable; coded 1 = baseline; 2 = 3-month follow-up; 3 = 6-month follow-up), and Anhedonia (MASQ AD scores at each time point). Second, to test the specificity of putative findings to anhedonia, we considered a model that also included non-anhedonic covariates (MASQ GDD, GDA and AA scores). Third, we considered a full model that also included a Time x Anhedonia interaction term. Models were fit using restricted maximum likelihood (REML) estimation, which provides unbiased estimates of the fixed effects while handling missing data (missing data were not imputed). Each model had two levels with Level 1 represented by observations nested within individuals and Level 2 represented by a subject-level random intercept. Models used a compound symmetric covariance structure. Degrees of freedom were estimated using Satterthwaite approximation. Continuous predictors were mean centered using the grand mean of the unipolar and bipolar mood disorder groups and scaled prior to analysis so that they had a mean of 0 and a standard deviation of 1. For all models predicting...
outcomes on the SF-36 MCS and PCS subscales, the alternate subscale of the SF-36 was also included as a covariate.

After establishing the association between anhedonia severity and quality of life outcomes, we performed a second stage of analysis where we evaluated ΔRewP markers as predictors of quality of life outcomes. We examined the main effect of ΔRewP amplitude and ΔRewP-related ΔACC CSD, as well as the interaction between these predictors and Time. The rationale for this was based on prior studies indicating that RewP amplitude measured at a single point in time prospectively predicts the course of depression longitudinally [35]. Model equations are shown in the Supplement.

Model selection: A likelihood-ratio test (LRT) and was used to determine whether a more complex model resulted in an improved model fit relative to a simpler model. The presence of multicollinearity was assessed by examining the VIF values for all main effects, and values < 4.0 were deemed acceptable.

Type I error control: Our modeling procedure resulted in 3 (predictors of interest: anhedonia, ΔRewP amplitude, ΔRewP-related ΔACC CSD) × 3 (outcomes: PCS, MCS, Q-LES-Q) best fitting models. The type I error rate was controlled using a Benjamini-Hochberg correction with the recommended false discovery rate of 0.1 [47].

Mediation analyses: As we reported in our prior paper, ΔRewP amplitude correlated with anhedonia severity [26]. Accordingly, in the third stage of our analysis we performed mediation models using the SPSS PROCESS macro [48] to determine whether any relationship between ΔRewP markers and quality of life was mediated by changes in anhedonia.

Group differences within the patient sample: We also conducted exploratory analyses to assess group differences in quality of life, anhedonia, and ΔRewP markers between those with unipolar and bipolar mood disorders. These analyses were conducted using one-way Analysis of Variance (ANOVA), with the healthy control group functioning as a normative comparison. The SF-36 subscales violated assumptions of homogeneity of variance, so Welch’s ANOVA was used for these subscales. For models where patient groups differed on quality of life, we evaluated whether any differences were mediated by anhedonia severity or ΔRewP markers. Data were verified to ensure that the assumptions for statistical tests used were met.

RESULTS

Sample characteristics

The sample (n = 112) was 63.4% female (n = 71), with a mean age of 28.6 (SD = 9.1, range 18–60). Among the patient group (n = 80), 72.5% (n = 58) had a unipolar mood disorder diagnosis (MDD/dysthymia, or MDD in partial remission), and 27.5% (n = 22) had a bipolar mood disorder diagnosis (BD-I/II, depressed, mixed or hypomanic). Furthermore, 40% (n = 32) took medication. Sample characteristics are shown in Table 1. The unipolar and bipolar mood disorder groups did not differ significantly on markers of illness severity (Table S1).

Worse anhedonia is linked to reduced quality of life cross-sectionally and longitudinally

Anhedonia, life enjoyment and satisfaction, and mental health-related quality of life changed significantly over time, whereas physical health-related quality of life remained relatively stable (Supplementary Results 2.1, Fig. S2). Bivariate Pearson’s correlations between anhedonia and quality of life measures at baseline (Fig. 2), and repeated measures correlations between anhedonia and quality of life measures longitudinally (Fig. S3), indicated that anhedonia was the strongest correlate of mental health-related quality of life, as well as life enjoyment and satisfaction, at baseline and at each of the longitudinal follow-up timepoints.

The results of the first stage of linear mixed effect modeling, including the best fitting models for each outcome, are shown in Table 2. The main effect of Anhedonia was significant across all models (all ps < 0.05), indicating that, when controlling for mood disorder polarity, or when additionally controlling for non-anhedonic symptoms of depression and anxiety, anhedonia was associated with variability in multiple aspects of quality of life. When considering model fit, the best fitting models for physical health-related quality of life, and life enjoyment and satisfaction, were those that contained the main effect of Anhedonia and the non-anhedonic covariates (Models 1B and 3B). These models showed that more severe anhedonia was associated with poorer physical health-related quality of life, and poorer life enjoyment and satisfaction, on average, over time. Specifically, levels of anhedonia 1 standard deviation above the mean were associated with physical health-related quality of life scores that were approximately 3.7 points lower (-3.65) and life enjoyment and satisfaction scores that were approximately 5.5 points lower (-5.49).

For mental health-related quality of life, the best fitting model was the model that contained the additional Time × Anhedonia interaction term (Model 2C). Here, reductions in anhedonia

Table 1. Sample characteristics.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Healthy Control (n = 32)</th>
<th>Mood Disorder (n = 80)</th>
<th>Test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M (SD)</td>
<td>28.4 (7.7)</td>
<td>28.7 (9.7)</td>
<td>t = 0.16</td>
<td>0.87</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>17 (53.1)</td>
<td>54 (67.5)</td>
<td>χ² = 2.04</td>
<td>0.15</td>
</tr>
<tr>
<td>Years education, M (SD)</td>
<td>17.0 (3.2)</td>
<td>15.9 (2.9)</td>
<td>t = 1.81</td>
<td>0.07</td>
</tr>
<tr>
<td>White, N (%)</td>
<td>21 (65.6)</td>
<td>59 (73.8)</td>
<td>χ² = 0.74</td>
<td>0.39</td>
</tr>
<tr>
<td>Hispanic, N (%)</td>
<td>2 (6.3)</td>
<td>8 (10.0)</td>
<td>χ² = 0.40</td>
<td>0.53</td>
</tr>
<tr>
<td>Mood symptom severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MASQ Anhedonic Depression, M (SD)</td>
<td>43.9 (11.0)</td>
<td>79.9 (12.4)</td>
<td>t = 14.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MASQ General Distress Depression, M (SD)</td>
<td>13.7 (3.7)</td>
<td>36.9 (10.9)</td>
<td>t = 11.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MASQ General Distress Anxiety, M (SD)</td>
<td>12.5 (2.4)</td>
<td>23.3 (7.0)</td>
<td>t = 8.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MASQ Anxious Arousal, M (SD)</td>
<td>17.6 (1.0)</td>
<td>25.8 (8.1)</td>
<td>t = 5.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health-related QoL (SF-36 PCS), M (SD)</td>
<td>55.7 (3.2)</td>
<td>52.8 (8.7)</td>
<td>t = 1.89</td>
<td>0.06</td>
</tr>
<tr>
<td>Mental health-related QoL (SF-36 MCS), M (SD)</td>
<td>56.6 (2.7)</td>
<td>26.2 (9.6)</td>
<td>t = 17.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Life enjoyment and satisfaction (Q-LES-Q), M (SD)</td>
<td>61.0 (6.2)</td>
<td>38.7 (8.8)</td>
<td>t = 13.00</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MASQ Mood and Anxiety Symptom Questionnaire, SF-36 Short Form-36 Scale, PCS Physical component summary score of the SF-36, MCS Mental component summary score of the SF-36, QoL Quality of life, Q-LES-Q Quality of Life, Enjoyment and Satisfaction Questionnaire.
severity over time were associated with improvements in mental health-related quality of life longitudinally. Specifically, the magnitude and sign of the interaction term (−1.14) indicated that a 1 standard deviation reduction in anhedonia severity was associated with an increase in mental health-related quality of life of 4.2 points over the 6 months of follow-up \[0.97 - 1.14 \times (-1) = 2.11 \text{ points per 3-month interval}\], whereas a 1 standard deviation increase in anhedonia severity was associated with a very modest decrease in mental health-related quality of life of 0.3 points over the 6 months of follow-up \[0.97 - 1.14 \times (1) = -0.17 \text{ points per 3-month interval}\].

Greater reward-related neural activation is associated with improvements in quality of life longitudinally via improvements in anhedonia

Of the 80 patients with quality of life data, 66 had valid ERP data (50 unipolar, 16 bipolar) and were included in the second stage of modeling.

ΔRewP amplitude as a predictor of quality of life. The results of our linear mixed effect modeling examining ΔRewP amplitude as a predictor of quality of life are shown in Table S2. The best fitting model for physical health-related quality of life was the model that contained the Time x ΔRewP interaction term (Model 4B). In this model, a 1 standard deviation increase in ΔRewP amplitude at baseline was associated with an increase in physical health-related quality of life of approximately 5 points over the 6 months of follow-up \[1.46 + 1.06 \times (1) = 2.52 \text{ points per 3-month interval}\], whereas a 1 standard deviation decrease in ΔRewP amplitude at baseline was associated with a smaller increase of 0.8 points over the 6 months of follow-up \[1.46 + 1.06 \times (-1) = 0.4 \text{ points per 3-month interval}\]. In contrast, the best fitting models for mental health-related quality of life, and life enjoyment and satisfaction, were the models that contained only the main effect of ΔRewP amplitude (Models 5A and 6A). In these models, ΔRewP amplitude that was 1 standard deviation above the mean was associated with mental health-related quality of life

Fig. 2 Associations between anhedonia, reward-related neural markers, and quality of life. Bivariate correlations between symptom severity, reward markers, and quality of life (a), ranked correlates of life enjoyment and satisfaction (b), ranked correlates of mental health-related quality of life (c), and ranked correlates of physical health-related quality of life (d). Correlations reflect associations among the patient group only. Color scale reflects Pearson’s r values with uncorrected p-values shown in parentheses in a. Asterisks on b, c, and d indicate significant correlations (⁎ p < 0.05; ⁎⁎ p < 0.01; ⁎⁎⁎ p < 0.001); all remain significant after Benjamini-Hochberg correction for multiple correlations. QLES Total scores on the Q-LES-Q, MCS Mental health-related quality of life subscale of the SF-36, PCS Physical health-related quality of life subscale of the SF-36, AD Anhedonic Depression subscale of the MASQ, GDD General Distress due to Depression subscale of the MASQ, GDA General Distress due to Anxiety subscale of the MASQ, AA Anxious arousal subscale of the MASQ, RewP ΔRewP amplitude, dACC ΔRewP-related current source density in the dorsal anterior cingulate cortex.
Table 2. Results of linear mixed effect models examining associations between anhedonia and quality of life in patients.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PCS</th>
<th>MCS</th>
<th>QLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>Model 1A</td>
<td>Model 1B</td>
<td>Model 1C</td>
</tr>
<tr>
<td>Dx</td>
<td>-0.67</td>
<td>-0.88</td>
<td>-0.92</td>
</tr>
<tr>
<td></td>
<td>[-4.03 to 2.69]</td>
<td>[-3.97 to 2.21]</td>
<td>[-4.01 to 2.18]</td>
</tr>
<tr>
<td>PCS</td>
<td>-3.30 ***</td>
<td>-3.43 ***</td>
<td>-3.30 ***</td>
</tr>
<tr>
<td>Time</td>
<td>0.71</td>
<td>0.73</td>
<td>-0.72</td>
</tr>
<tr>
<td></td>
<td>[-0.23 to 1.66]</td>
<td>[-0.21 to 1.67]</td>
<td>[-0.22 to 1.66]</td>
</tr>
<tr>
<td>AD</td>
<td>-3.72 ***</td>
<td>-3.65 ***</td>
<td>-4.47**</td>
</tr>
<tr>
<td>GD</td>
<td>0.28</td>
<td>0.36</td>
<td>-2.80**</td>
</tr>
<tr>
<td></td>
<td>[-1.40 to 1.96]</td>
<td>[-1.33 to 2.05]</td>
<td>[-4.39 to -1.21]</td>
</tr>
<tr>
<td>GA</td>
<td>-0.19</td>
<td>-0.15</td>
<td>-1.71*</td>
</tr>
<tr>
<td></td>
<td>[-1.85 to 1.47]</td>
<td>[-1.81 to 1.52]</td>
<td>[-3.28 to -0.14]</td>
</tr>
<tr>
<td>AA</td>
<td>-2.44**</td>
<td>-2.47**</td>
<td>-0.55</td>
</tr>
<tr>
<td></td>
<td>[-3.89 to -0.99]</td>
<td>[-3.92 to -1.02]</td>
<td>[-2.00 to 0.91]</td>
</tr>
<tr>
<td>Time x AD</td>
<td>0.42</td>
<td>-1.14*</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Model statistics

| Marg. R² | 0.135 | 0.225 | 0.225 | 0.644 | 0.716 | 0.721 | 0.646 | 0.688 | 0.687 |
| Cond. R² | 0.628 | 0.621 | 0.622 | 0.767 | 0.799 | 0.803 | 0.833 | 0.845 | 0.844 |
| ICC      | 0.57  | 0.51  | 0.51  | 0.35  | 0.29  | 0.30  | 0.53  | 0.50  | 0.50  |
| AIC      | 1412.3 | 1398.7 | 1400.0 | 1429.2 | 1391.1 | 1388.5 | 1294.3 | 1279.2 | 1281.2 |

PCS physical health component of the SF-36, MCS mental health component of the SF-36, QLES Quality of Life Enjoyment and Satisfaction Questionnaire, Dx diagnosis (0 = unipolar; 1 = bipolar), GDD General Distress Depression MASQ subscale, GDA General Distress Anxiety MASQ subscale, AA Anxious Arousal MASQ subscale, AD Anhedonic Depression MASQ subscale, AIC Akaike information criterion.

***p < 0.001; **p < 0.01; *p < 0.05.

*aDenotes the best fitting model for each outcome.
scores that were approximately 3.1 points higher (3.07) and life enjoyment and satisfaction scores that were 2.4 points higher (2.41).

Mediation analyses evaluated whether change in anhedonia from baseline to 3 months or from baseline to 6 months mediated the link between ∆RewP amplitude and improvements in physical health-related quality of life over time, however, mediation models were not significant (bootstrapped 95% confidence intervals for indirect effects contained zero).

\[ \Delta \text{RewP-related dACC CSD} \] as a predictor of quality of life. The results of our linear mixed effect modeling examining ∆RewP-related dACC CSD as a predictor of quality of life are shown in Table S3. The best fitting model for physical health-related quality of life was the model that contained only the main effect of ∆RewP-related dACC CSD (Model 7A), however in this model ∆RewP-related dACC CSD was not a significant predictor of physical health-related quality of life. In contrast, the best fitting models for mental health-related quality of life, and life enjoyment and satisfaction, were the models that contained the Time x ∆RewP-related dACC CSD interaction term (Models 8B and 9B). Here, stronger ∆RewP-related dACC CSD at baseline was associated with greater improvements in mental health-related quality of life, and in life enjoyment and satisfaction, over time. Specifically, a 1 standard deviation increase in ∆RewP-related dACC CSD was associated with an increase in mental health-related quality of life of 12.3 points over the 6 months of follow-up \[ (4.09 + 2.05 \times (1) = 6.14 \text{ points per 3-month interval}) \], whereas a 1 standard deviation decrease in ∆RewP-related dACC CSD was associated with a smaller increase of 4.1 points over the 6 months of follow-up \[ (4.09 + 2.05 \times (-1) = 2.04 \text{ points per 3-month interval}) \]. Similarly, a 1 standard deviation increase in ∆RewP-related dACC CSD was associated with an increase in life enjoyment and satisfaction of 10 points over the 6 months of follow-up \[ (3.60 + 1.70 \times (1) = 5 \text{ points per 3-month interval}) \], whereas a 1 standard deviation decrease in ∆RewP-related dACC CSD at baseline was associated with a smaller increase of 3.8 points over the 6 months of follow-up \[ (3.60 + 1.70 \times (-1) = 1.9 \text{ points per 3-month interval}) \].

Mediation analyses showed that associations between ∆RewP-related dACC CSD and longitudinal improvements in mental health-related quality of life (MCS) at 3- and 6-month follow-up were mediated by improvements in anhedonia over the same time periods (Supplementary Results 2.2, Fig. S4). The same pattern of results emerged for the Q-LES-Q. Results remained significant when controlling for non-anhedonic symptoms of depression (MASQ GDD), indicating that effects were specific to anhedonia rather than depressive symptoms more generally.

**Differences in quality of life as a function of mood disorder polarity**

Group differences in quality of life between the groups are shown in Fig. S5. Compared to those with a bipolar mood disorder, those with a unipolar mood disorder reported significantly lower life enjoyment and satisfaction (Q-LES-Q), and this difference was mediated by more severe anhedonia (Supplementary Results 2.3–2.4, Fig. S6).

**DISCUSSION**

This study examined whether anhedonia and its reward-related neural correlates were associated with changes in quality of life among individuals seeking treatment for mood disorders. Several novel findings emerged. First, worse anhedonia was associated with poorer physical health-related quality of life, poorer mental health-related quality of life, and poorer life enjoyment and satisfaction, cross-sectionally. Furthermore, changes in anhedonia predicted changes in mental health-related quality of life over time, even when controlling for non-anhedonic symptoms of depression and anxiety. Second, neural markers of reward responsiveness (∆RewP amplitude and ∆RewP-related dACC CSD) at baseline were linked to different facets of quality of life cross-sectionally and longitudinally. Specifically, stronger ∆RewP amplitude was associated with better mental health-related quality of life and better life enjoyment and satisfaction, on average, as well as greater improvements in physical health-related quality of life over time. ∆RewP-related dACC CSD was also associated with quality of life, albeit in a somewhat different manner than ∆RewP amplitude. Specifically, although ∆RewP-related dACC CSD was not associated with physical health-related quality of life, stronger ∆RewP-related dACC CSD predicted greater improvements in mental health-related quality of life, as well as greater improvements in life enjoyment and satisfaction, over time, and these associations were mediated by improvements in anhedonia. Finally, compared to individuals with a bipolar mood disorder, those with a unipolar mood disorder had poorer life enjoyment and satisfaction, and this difference was mediated by more severe anhedonia. Taken together, these findings indicate that anhedonia and its neural correlates are critical factors underpinning variability in quality of life among individuals with mood disorders.

Our findings are consistent with prior work showing that anhedonia is associated with a range of adverse outcomes that compound the burden of depression, including poorer treatment response [16–19], greater comorbidity [12, 13], greater suicidality [11], and greater psychosocial impairment [5]. Our data also align with studies highlighting links between reward-related neural correlates of anhedonia and greater depression morbidity (e.g., recurrence and suicidality; [32, 33]). Importantly, our findings extend existing research by showing that anhedonia and its neural correlates are linked to cross-sectional and longitudinal variability in individuals’ subjective perception of their mental health and the degree to which it interferes with daily life. This suggests that addressing anhedonia more effectively and possibly normalizing aberrant brain reward function through treatment could be an important pathway through which the subjective burden of mood disorders could be reduced.

It is not surprising that anhedonia and its neural correlates emerged as prominent predictors of quality of life, considering the broad impact hedonic disturbances have across multiple life domains. For example, the Q-LES-Q infers quality of life by probing satisfaction across domains such as social relationships, work, and leisure activities [40], and qualitative studies also indicate that these domains are prioritized by individuals and their families seeking treatment for depression [15]. In parallel, there is a wealth of evidence showing that anhedonia has a profound impact on a person’s ability to process social rewards, their desire to work for reward, and their ability to anticipate pleasure from leisure activities (for a review, see [10]). When viewed through the lens of Wilson and Cleary’s Conceptual Model of Patient Outcomes, anhedonia impacts domains of functioning that influence an individual’s perception of social connectedness, sense of meaning and purpose, and enjoyment in life (Fig. 3). Accordingly, individuals who experience ongoing anhedonia, even when other symptoms of depression remit, are likely to be at risk of poorer longer-term outcomes.

Our findings have important implications for improving health outcomes for people with depression. Specifically, they indicate that clinical trials using outcome measures focused predominantly on reductions in global depressive symptom severity may fail to capture treatment effects on illness features that are pivotal to remission. Assessing anhedonia, along with functioning in life domains most directly impacted by anhedonia, may enhance our ability to identify treatments that more effectively reduce depression-related disability. Furthermore, our findings reiterate the importance of developing treatments that are more effective
for anhedonia and reward-related disturbances. To date, several novel mechanisms have attracted interest as promising treatment targets for anhedonia, including kappa opioid receptor antagonism and potassium channel modulation [49]. Further research is needed to determine whether these novel treatments impact broader patient outcomes, such as quality of life.

Some limitations of our study should be noted. Although our longitudinal design is a strength, the data span a relatively short follow-up period and ERP data were only available at baseline. An important question is whether normalization of aberrant brain reward activation and resolution of anhedonic symptoms are associated with improvements in quality of life that are sustained over longer time periods. Such longitudinal studies would help strengthen inferences regarding potential causal pathways linking anhedonia and its neural correlates to quality of life. Furthermore, the limited number of individuals with bipolar mood disorders in our sample means that we were likely underpowered to detect group-specific effects. Further examination of the relationship between anhedonia and quality of life in individuals with bipolar mood disorders is therefore warranted. Finally, although we expected ΔRewP amplitude and ΔRewP-related dACC CSD would probe overlapping neural processes, these two variables exhibited slightly different patterns of association with the distinct quality of life measures. Given that scalp-level ERPs can be generated by neural activity spread across a wide network of brain regions, one possibility is that scalp-level ΔRewP amplitude reflects a wider range of neural processes than ΔRewP-related dACC CSD. Furthermore, if scalp-level ΔRewP amplitude is driven by additional factors beyond those specifically involved in reward processing, this may explain why anhedonia did not mediate the link between ΔRewP amplitude and physical health-related quality of life, in the same manner that it mediated the link between ΔRewP-related dACC CSD and mental health-related quality of life. Future research should investigate this hypothesis.

To conclude, this study found that anhedonia and neural markers of reward processing were associated with important aspects of quality of life cross-sectionally and longitudinally in individuals with mood disorders, independently of non-anhedonic symptoms of depression or anxiety. Our findings highlight the importance of accelerating efforts in the field of novel anti-anhedonic treatment discovery as a means for improving health outcomes in individuals living with depression.

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AUTHOR CONTRIBUTIONS
DAP, AEW and MTT contributed to the study conception and design; AEW, AVR, and ML contributed to acquisition of the data; AEW, PK, DF and FD contributed to data analyses; AEW, GF and DAP contributed to statistical analyses and were responsible for data interpretation. AEW drafted the manuscript, and all authors critically reviewed the manuscript and made important intellectual contributions. DAP secured funding and provided overall supervision for the project.

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COMPETING INTERESTS
Over the past 3 years, DAP has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neuromora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Otsuka, Sage Therapeutics, Sunovion, and Takeda; he has received honoraria from the Psychonomic Society and American Psychological Association (for editorial work) and Alkermes; he has received research funding from the Bird Foundation, Brain and Behavior Research Foundation, Dana Foundation, Millennium Pharmaceuticals, National Institute of Mental Health (NIMH), and Wellcome Leap (Multi-Channel Psych); he has received stock options from Compass Pathways, Engrail Therapeutics, Neuromora Therapeutics, and Neuroscience Software. DAP has a financial interest in Neuromora Therapeutics (formerly BlackThorn Therapeutics), which has licensed the copyright to the Probabilistic Reward Task through Harvard University. DAP’s interests were reviewed and are managed by McLean Hospital and Massachusetts General Brigham in accordance with their conflict-of-interest policies. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. In the past 3 years, Michael Treadway has served as a paid consultant for Neumora Therapeutics (formerly BlackThorn Therapeutics) and Boehringer Ingelheim. All other authors report no financial relationships with commercial interest.

ADDITIONAL INFORMATION
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Correspondence and requests for materials should be addressed to Diego A. Pizzagalli.