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

Diego Pizzagalli (dap@mclean.harvard.edu)
Harvard Medical School/McLean Hospital https://orcid.org/0000-0002-7772-1143
Alexis Whitton
Department of Psychiatry, McLean Hospital/Harvard Medical School https://orcid.org/0000-0002-7944-2172
Poornima Kumar
McLean Hospital https://orcid.org/0000-0002-9548-3281
Michael Treadway
Emory University https://orcid.org/0000-0002-5913-114X
Ashleigh Rutherford
Manon Ironside
Dan Foti
Garrett Fitzmaurice
Fei Du
McLean Hospital, Harvard Medical School https://orcid.org/0000-0002-9549-4255

Article

Keywords:

Posted Date: November 16th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2247153/v1

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Version of Record: A version of this preprint was published at Molecular Psychiatry on July 4th, 2023. See the published version at https://doi.org/10.1038/s41380-023-02165-1.

Abstract

Leading professional health bodies have called for the wider adoption of Patient Reported Outcome Measures, such as quality of life, in research and clinical practice as a means for understanding why the global burden of depression continues to climb despite 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.

ClinicalTrials.gov identifier: NCT01976975

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 symptomatic improvement (4, 5), suggesting that overall symptom abatement may be insufficient for improving health outcomes.

Accordingly, the Organisation for Economic Co-operation and Development, World Health Organization, National Institute of Health, and others, have urged for the broader adoption of patient-reported outcomes measures (PROMs) in research and clinical practice as a means for promoting patient-centered care and improving treatment outcomes (6–8). In addition to symptoms, PROMs assess a patient's holistic perceptions of their own illness burden, and capture features such as health-related quality of life, satisfaction, and enjoyment, 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 clinical and functional outcomes and is likely an important factor contributing to depression-related disease burden (10). Even after controlling for overall depressive symptom severity, more severe anhedonia uniquely predicts greater psychosocial and functional impairment (5), increased suicidal ideation (11), greater psychiatric (12) and medical (13) comorbidity, as well as increased caregiver stress (14). Anhedonia and its corollaries (e.g., loss of motivation) are also a top treatment priority for healthcare providers and consumers due to the profound impact these illness features have 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, therefore, crucial for identifying treatment targets that can improve outcomes for people with depression.

Anhedonia is a multifaceted construct linked to impairments in aspects of reward processing (10) that are subsumed under the Research Domain Criteria's (RDoC) Positive Valence Systems (PVS; 20). The RDoC PVS subdomain of reward learning

has emerged as an especially promising candidate for improving our understanding of anhedonia pathophysiology given that it correlates with anhedonia severity cross-sectionally and prospectively (21, 22) and covaries with treatment-related improvements in anhedonic symptoms (23). Although no studies have specifically examined links between PVS indices of reward learning and quality of life, findings from a recent longitudinal study provides 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 young adults seeking treatment for psychological distress. Stronger reward prediction error signals predicted greater improvements in psychosocial functioning over six months, and this improvement was mediated specifically by improvements in anhedonia (24). These findings suggest that reward learning and the underlying neurocircuitry may be an important target for novel treatments that could improve outcomes in individuals with depression.

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 treatment-seeking 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 frontocentral positive deflection in the 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). Critically, the RewP is blunted in individuals with acute (28) and remitted (29) depression, predicts depression onset (30), and is predictive of a range of depressive illness features associated with increased morbidity, including chronicity and recurrence (31), as well as suicidal ideation (32). However, no study has examined whether the RewP is associated with PROMs, such as quality of life.

To address this knowledge gap, the aim of this study was to examine whether RewP amplitude (scalp-level), RewP-related activation in the ACC (source localized), and anhedonia severity, were linked to variation in quality of life among individuals seeking treatment for mood disorders cross-sectionally and longitudinally. In doing so, we were informed by the conceptual model of patient outcomes proposed by Wilson and Cleary (33), 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.

Materials And Methods

Study design

Data used for this analysis were collected as part of a broader longitudinal naturalistic study examining reward learning in individuals with mood disorders, which we have described in detail previously (26). This broader study implemented a novel recruitment strategy wherein, rather than DSM diagnoses, participants were recruited based on their performance on a behavioral probabilistic reward task (PRT; 21) that evaluates the degree to which an individual modulates their behavior as a function of prior reinforcement (see Supplemental Methods 1.1.-1.2.). As part of this broader study, healthy controls and individuals seeking treatment for mood disorders were first invited to undergo screening on the PRT to determine their eligibility. Screening continued until two conditions were met: 1) 32 healthy controls who had valid PRT data and who met the broader study eligibility were recruited, and 2) 80 individuals with unipolar or bipolar mood pathology whose PRT performance spanned the full range of a normative distribution, and who met inclusion the broader study eligibility criteria, were recruited. Details of the final sample's PRT performance has been reported in our prior paper (26). Eligible participants completed five study visits: 1) PRT screening and diagnostic assessment, 2) baseline EEG/ERP recording, 3) baseline MRI

scan, 4) a 3-month clinical follow-up assessment, and 5) a 6-month clinical follow-up assessment. This novel approach to recruitment meant that the full range of reward learning performance – ranging from blunted reward learning to rapid reward learning – 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 clinical symptom trajectories, as reported in our prior paper (26).

In this prior paper, we found that the RewP was associated with variability in anhedonia severity. The current study critically 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. The RewP (measured at both the scalp-level and using source localization), anhedonia severity, and quality of life, were all assessed at baseline, and anhedonia severity and quality of life was assessed again at the 3- and 6-month follow-up assessments.

Participants

Adults seeking treatment for mood disorders (n = 80) were recruited through clinics at Massachusetts General Hospital and McLean Hospital, and healthy controls (n = 32) were recruited from the community. To be eligible to participate, all participants had to be fluent in English, have normal or corrected-to-normal vision, and be right-handed. Exclusionary criteria for all participants included: current illicit drug use (as indicated by a positive urine drug screen on the day of testing), history of chronic migraine or seizure disorder, or a history of significant head injury or loss of consciousness for two minutes or longer. Inclusion criteria for individuals in the mood disorders group were: mood-related psychopathology (e.g., depression, mixed episode, or hypomania) severe enough to cause distress/impairment, as assessed via the Structured Clinical Interview for DSM-IV-TR (34). Although treatment was not provided as part of this study, participants could pursue treatment while participating provided that the treatment was not on a list of exclusionary treatments (these included any treatments known to have potent effects on striatal dopamine; Supplemental Methods 1.3–1.4). Exclusion criteria for individuals in the mood disorders group were: electroconvulsive therapy in the past two years, psychosis or other exclusionary comorbidities (Supplemental Methods 1.3–1.4). Inclusion criteria for the healthy control group were: absence of any 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 (35) score less than 10. Healthy controls were excluded if they had recently taken any of the exclusionary medications (Supplemental Methods 1.3). 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 (33), 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 (36) 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 (e.g., energy and fatigue), social functioning, role limitations due to emotional problems, and mental health. Items for each domain are summed and converted to a scale from 0 (worst) to 100 (best). These domain scores can be 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 (37).

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

The Q-LES-Q (38) 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 and family 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. Following standard procedures, the first 14 items were summed to create a total score (ranging from 14 to 70), which was expressed as a percentage based on the maximum total score of the items completed (0–100). The normal range of scores observed in community samples is 70–100 (38).

Measures Of Symptom Severity

Mood and anxiety symptoms were assessed using the 62-item Mood and Anxiety Symptom Questionnaire (39), which allows dissociation of symptoms of anhedonia from non-anhedonic symptoms of depression as well as anxiety. The measure is comprised of 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

As part of our broader study (26), we examined multiple neural reward learning markers as predictors of longitudinal symptom trajectories (an overview of the broader study’s methodology is described in the Supplemental Methods 1.5–1.6). For the current study, we focused our analyses specifically on the link between quality of life and the RewP, given that in the broader study, the RewP was the neural reward learning marker that correlated with anhedonia severity. However, for completeness, we also describe exploratory analyses examining links between quality of life and the other two neural markers evaluated in this broader study, in the Supplemental Results 2.5. In the current study we examined variation in RewP using two metrics – ΔRewP amplitude and ΔRewP-related dACC CSD:

ΔRewP amplitude

The RewP on 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 kW). Following pre-processing (Supplemental Methods), a temporospatial PCA was used to separate the RewP from overlapping ERP components. Temporal variance in the averaged ERP waveforms was examined using temporal PCA and Infomax rotation. Based on the resulting scree plot, 12 temporal factors were retained for rotation. The spatial distribution of these temporal factors was then examined using spatial PCA and Infomax rotation, with a spatial PCA conducted for each temporal factor. Eight spatial factors were retained for each temporal factor. Analyses focused on the PCA component with timing and topography most consistent with the RewP (TF8/SF2; see Fig. 1). The difference in RewP amplitude following feedback on lean versus rich trials was then computed to yield our first metric of neural reward responsiveness (‘ΔRewP amplitude’). The difference score was used because it 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) (40) was used to capture 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 then 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 then extracted for rich and lean trials, and then a difference score computed to yield our second metric of reward responsiveness ('ΔRewP-related dACC CSD').

---Insert Fig. 1 about here---

Statistical analysis

Bivariate associations

Analyses were conducted using R version 4.2.1 in RStudio (41). Pearson's correlations were used to examine the bivariate associations between anhedonia, ΔRewP amplitude, ΔRewP-related dACC CSD, and quality of life at baseline. These bivariate baseline correlations were supplemented with repeated measures correlations, conducted using the *rmcorr* package (42), which assessed the common intraindividual correlation between anhedonia and quality of life measures at the three assessment time points. Benjamini-Hochberg correction was used to correct for multiple correlations (43).

Longitudinal associations

Model-building. Following assessment of the bivariate associations, hierarchical linear mixed effect modeling was used to examine the relationship between anhedonia severity, *Δ*RewP markers, and changes in quality of life over time. This was implemented using the *lme4* package (44) and was conducted in two stages. In the first stage, we examined the association between anhedonia severity 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* (coded 1 = baseline; 2 = 3-month follow-up; 3 = 6-month follow-up), and *Anhedonia* (MASQ AD scores). 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. Each model included subject-level random intercepts, continuous predictors were mean-centered prior to analysis, and 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. These three models predicting quality of life outcomes (y) were specified using the R notation:

(1) y ~ Diagnosis + Time + AD + (1|Participant)

(2) y ~ Diagnosis + Time + AD + GDD + GDA + AA (1|Participant)

(3) y ~ Diagnosis + GDD + GDA + AA + Time*AD + (1|Participant)

After establishing the association between anhedonia severity and quality of life outcomes, we performed a second stage of analysis where models were built using ΔRewP amplitude and ΔRewP-related dACC CSD as predictors of quality of life outcomes. These models were conducted in the subset of patients who had valid ERP data. The models evaluated in this second analysis stage were specified using the R notation:

(1) y ~ Diagnosis + Time + *Δ*RewPamp (or *Δ*RewPdACC) + (1|Participant)

(4) y ~ Diagnosis + Time**Δ*RewPamp (or Time**Δ*RewPdACC) + (1|Participant)

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 more complex model was chosen if the LRT was significant and the

Akaike information criterion (AIC) was lower than the 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. The linear mixed effect modeling procedure employed for this study resulted in 3 (predictors of interest: anhedonia, ΔRewP amplitude, ΔRewP-related dACC CSD) x 3 (outcomes: PCS, MCS, Q-LES-Q) best fitting models. To control the type I error rate when examining the significance of individual predictors within these nine models, we used the Benjamini-Hochberg correction with the recommended false discovery rate of 0.1 (45).

Mediation analyses

As we reported in our prior paper, ΔRewP amplitude was found to correlate with anhedonia severity (26). Accordingly, in the third stage of our analysis we performed mediation models using the SPSS PROCESS macro (46) to determine whether any relationship between ΔRewP amplitude or ΔRewP-related dACC CSD and quality of life was mediated by changes in anhedonia severity over the same time period.

Exploratory analysis of group differences within the patient sample

Although the primary focus of our analysis was on transdiagnostic associations between anhedonia and quality of life in individuals with mood disorders, we also conducted exploratory analyses to assess whether there were differences in quality of life, anhedonia severity, ΔRewP amplitude and ΔRewP-related dACC CSD between those with unipolar and bipolar mood disorders. These analyses were conducted using one-way Analysis of Variance, with the healthy control group functioning as a normative comparison. For models where patient groups differed on quality of life, we evaluated whether any differences were mediated by anhedonia severity, ΔRewP amplitude, or ΔRewP-related dACC CSD.

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 (see Table S1 for sub-group comparisons).

Table 1
Sample characteristics

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

Note. 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.

---Insert Table 1 about here---

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 (Supplemental Results 2.1, Fig. S1). 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. S2), indicated that anhedonia was the strongest correlate of mental health-related quality of life, as well as life enjoyment and satisfaction, both at baseline and at each of the longitudinal follow-up timepoints.

The results of the first stage of hierarchical 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 *p*s < 0.05), indicating that, when controlling for mood disorder polarity, or when additionally controlling for non-anhedonic symptoms of depression and anxiety, anhedonia severity was associated with variability in multiple aspects of quality of life. When considering model fit, we found that 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. For mental health-related quality of life, the best fitting model was the model that contained the additional *Time* x *Anhedonia* interaction term (Model 2C). Here, reductions in anhedonia severity over time were associated with improvements in mental health-related quality of life longitudinally.

Table 2
Results of linear mixed effect models examining associations between anhedonia and quality of life in patients

Outcome	**PCS**			**MCS**			**QLES**		
Model	Model 1A	Model 1B†	Model 1C	Model 2A	Model 2B	Model 2C†	Model 3A	Model 3B†	Model 3C
Fixed effects, Estimate [95% CI]									
Dx	-0.67	-0.88	-0.92	2.63	2.69*	2.72*	2.09	2.06	2.06
	[-4.03–2.69]	[-3.97–2.21]	[-4.01–2.18]	[-0.24–5.51]	[0.16–5.22]	[0.21–5.23]	[-0.31–4.49]	[-0.20–4.32]	[-0.20–4.32]
PCS				-3.30***	-3.43***	-3.30***			
				[-4.39 – -2.22]	[-4.45 – -2.41]	[-4.31 – -2.28]			
MCS	-4.51***	-5.07***	-4.95***						
	[-5.96 – -3.05]	[-6.61 – -3.53]	[-6.51 – -3.38]						
Time	0.71	0.73	-0.72	1.27*	0.96	0.97	1.65***	1.46***	1.46***
	[-0.23–1.66]	[-0.21–1.67]	[-0.22–1.66]	[0.20–2.34]	[-0.04–1.96]	[-0.02–1.96]	[0.94–2.35]	[0.77–2.16]	[0.76–2.16]
AD	-3.72***	-3.65***	-4.47**	-9.03***	-6.30***	-3.94**	-6.90***	-5.49***	-5.55***
	[-5.24 – -2.19]	[-5.28 – -2.03]	[-7.04 – -1.90]	[-10.17 – -7.88]	[-7.71 – -4.88]	[-6.54 – -1.33]	[-7.73 – -6.07]	[-6.57 – -4.41]	[-7.45 – -3.64]
GD		0.28	0.36		-2.80**	-2.91***		-1.54*	-1.54*
		[-1.40–1.96]	[-1.33–2.05]		[-4.39 – -1.21]	[-4.49 – -1.33]		[-2.75 – -0.33]	[-2.75 – -0.32]
GA		-0.19	-0.15		-1.71*	-1.75*		-0.70	-0.70
		[-1.85–1.47]	[-1.81–1.52]		[-3.28 – -0.14]	[-3.30 – -0.19]		[-1.91–0.52]	[-0.19–0.52]
AA		-2.44**	-2.47**		-0.55	-0.46		-0.45	-0.46
		[-3.89 – -0.99]	[-3.92 – -1.02]		[-2.00–0.91]	[-1.90–0.99]		[-1.53–0.62]	[-1.54–0.62]
Time x AD			0.42			-1.14*			0.02
			[-0.60–1.43]			[-2.19 – -0.08]			[-0.72–0.77]
Model statistics									
Marg. R^2	0.135	0.225	0.225	0.644	0.716	0.721	0.646	0.688	0.687

Note.†Denotes the best fitting model for each outcome. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

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.

Outcome	PCS			MCS			QLES		
Cond. R^2	0.628	0.621	0.622	0.767	0.799	0.803	0.833	0.845	0.844
AIC	1412.3	1398.7	1400.0	1429.2	1391.1	1388.5	1294.3	1279.2	1281.2

Note.†Denotes the best fitting model for each outcome. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

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.

---Insert Fig. 2 about here---

---Insert Table 2 about here---

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

Of the 80 patients with symptom and quality of life data, 66 had valid ERP data and were included in the second stage of modeling.

ΔRewP amplitude as a predictor of quality of life. The results of our hierarchical 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 amplitude* interaction term (Model 4B), where stronger ΔRewP amplitude at baseline was associated with greater improvements in physical health-related quality of life over time. 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). Here, stronger ΔRewP amplitude at baseline was associated with better mental health-related quality of life, as well as better life enjoyment and satisfaction, on average, across timepoints.

Mediation analyses evaluated whether change in anhedonia from baseline to 3 months or from baseline to 6 months mediated the link between ΔRewP 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).

ΔRewP-related dACC CSD as a predictor of quality of life. The results of our hierarchical linear mixed effect modeling examining ΔRewP-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 *ΔRewP-related dACC CSD* (Model 7A), however in this model ΔRewP-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 *ΔRewP-related dACC CSD* interaction term (Models 8B and 9B). Here, stronger ΔRewP-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.

Mediation analyses showed that associations between ΔRewP-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 severity over the same time periods (Supplemental Results 2.2, Fig. S3). The same pattern of results emerged for the Q-LES-Q, where associations between ΔRewP-related dACC CSD and longitudinal improvements in life enjoyment and satisfaction at 3- and 6-month follow-up were mediated by longitudinal improvements in anhedonia. Results remained

significant when controlling for non-anhedonic symptoms of depression (MASQ GDD), indicating that mediation 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 control, unipolar and bipolar mood disorder groups are shown in Fig. S4, along with group differences in anhedonia, ΔRewP amplitude and ΔRewP-related dACC CSD. Compared to those with a bipolar mood disorder, those with a unipolar mood disorder reported poorer mental health-related quality of life (MCS) and poorer life enjoyment and satisfaction (Q-LES-Q). Consistent with the longitudinal associations observed across the patient sample, poorer mental health-related quality of life in those with a unipolar mood disorder was driven primarily by more severe levels of anhedonia (Supplemental Results 2.3–2.4, Fig. S5).

—Insert Fig. 3 about here—

Discussion

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

The results from this study are consistent with prior work showing that even after controlling for overall depression severity, 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 more persistent psychosocial and functional impairment (5). Furthermore, our data align with prior studies highlighting links between reward-related neural correlates of anhedonia – namely, the RewP – and greater depression morbidity (e.g., recurrence and suicidality; 31, 32). Importantly however, the findings from our study extend this existing research by showing that anhedonia and its neural correlates are linked to cross-sectional and longitudinal variability in patients' subjective perception of their mental health and the degree to which it interferes with daily life. This suggests that better addressing anhedonic symptoms and possibly normalizing aberrant brain reward function through treatment may be an important pathway via which we can reduce the subjective burden of mood disorders.

It is not surprising that anhedonia and its neural correlates emerged as prominent correlates of quality of life, considering the broad impact that 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 (38), and qualitative studies also indicate that these domains are a critical aspect of depression management for patients and their families (15). In parallel, there is a wealth of evidence showing that anhedonia has 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 multiple domains of functioning that influence an individual's perception of social connectedness, sense of meaning and purpose, and enjoyment in life (Fig. 3). Accordingly, patients who experience ongoing anhedonia, even when other symptoms of depression remit, are likely to be at risk of poor longer-term outcomes.

Our findings have important implications for improving health outcomes for people with depression. Specifically, our results 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 can more effectively reduce depression-related disability and impairment. 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 (47). Further research is needed to determine whether these novel treatments impact broader patient outcomes, such as quality of life.

Some limitations must be considered when interpreting our findings. First, although the longitudinal design of our study is a strength, the data span a relatively short follow-up period and ERP data were only available at baseline. While promising, an important unanswered 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 to strengthen inferences regarding potential causal pathways linking anhedonia and its neural correlates to quality of life. Furthermore, although our sample included individuals with unipolar and bipolar mood disorders, the limited number of individuals with bipolar mood disorders 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.

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 broader health outcomes in individuals living with depression.

Declarations

Acknowledgements

We would like to acknowledge Thilo Deckersbach, Andrew Nierenberg, and Amy Farabaugh for facilitating recruitment of participants through the Depression Clinic and Research Program and the Bipolar Clinic and Research Program at Massachusetts General Hospital, as well as Daniel Ju Hyung Kim, Emily E. Bernstein, and Margaret E. Gigler for their assistance with patient screening and data collection at these two clinics. We would also like to thank Madeline M. Alexander, Laurie A. Scott, Nancy Hall-Brooks, and David J. Crowley for their important contributions to the screening and clinical assessment of participants recruited through the McLean Hospital Center for Depression, Anxiety and Stress Research.

Conflict of interest statement

Over the past 3 years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Otsuka, 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 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, Neumora Therapeutics, and Neuroscience Software. Dr. Pizzagalli has a financial interest in Neumora Therapeutics (former BlackThorn Therapeutics), which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr. Pizzagalli'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.

Funding

This work was funded by 1 1R01MH101521 and R37MH068376 (to DAP). In addition, DAP was partially supported by Wellcome Leap Multi-Channel Psych. AEW was supported by a C.J. Martin Early Career Fellowship from the National Health and Medical Research Council of Australia (GNT1110773).

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Figures

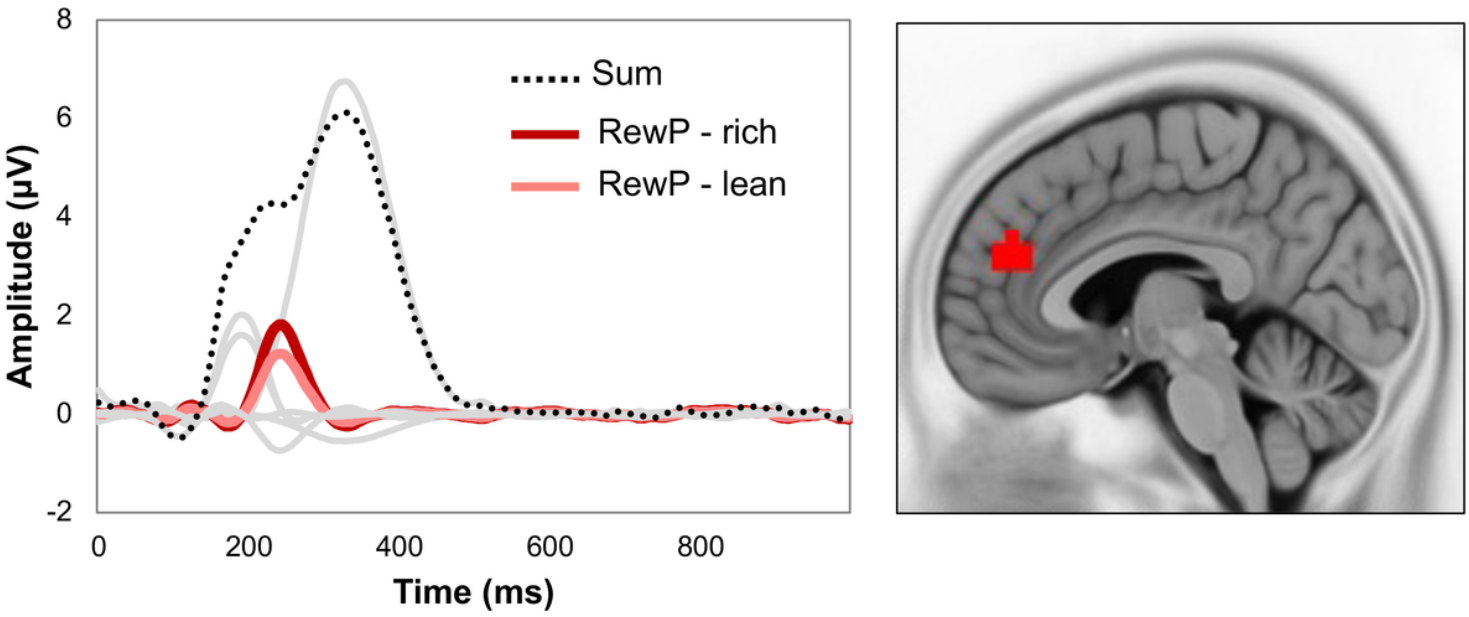

Figure 1

The waveform on the left shows key components identified by the principal component analysis (PCA). The black dotted line shows the waveform resulting from adding all key PCA components together, which closely resembles the raw ERP waveform. The two red lines show the RewP components (TF8/SF2) for the rich (higher amplitude) and lean (lower amplitude) conditions. The grey lines show other ERP components that were derived from the PCA, but which were not the focus of this analysis. The results of the source localization analysis (shown on the right) indicated that the scalp recorded RewP component was associated with current source density (CSD) in a cluster of voxels in the dorsal anterior cingulate cortex (dACC), shown in red.

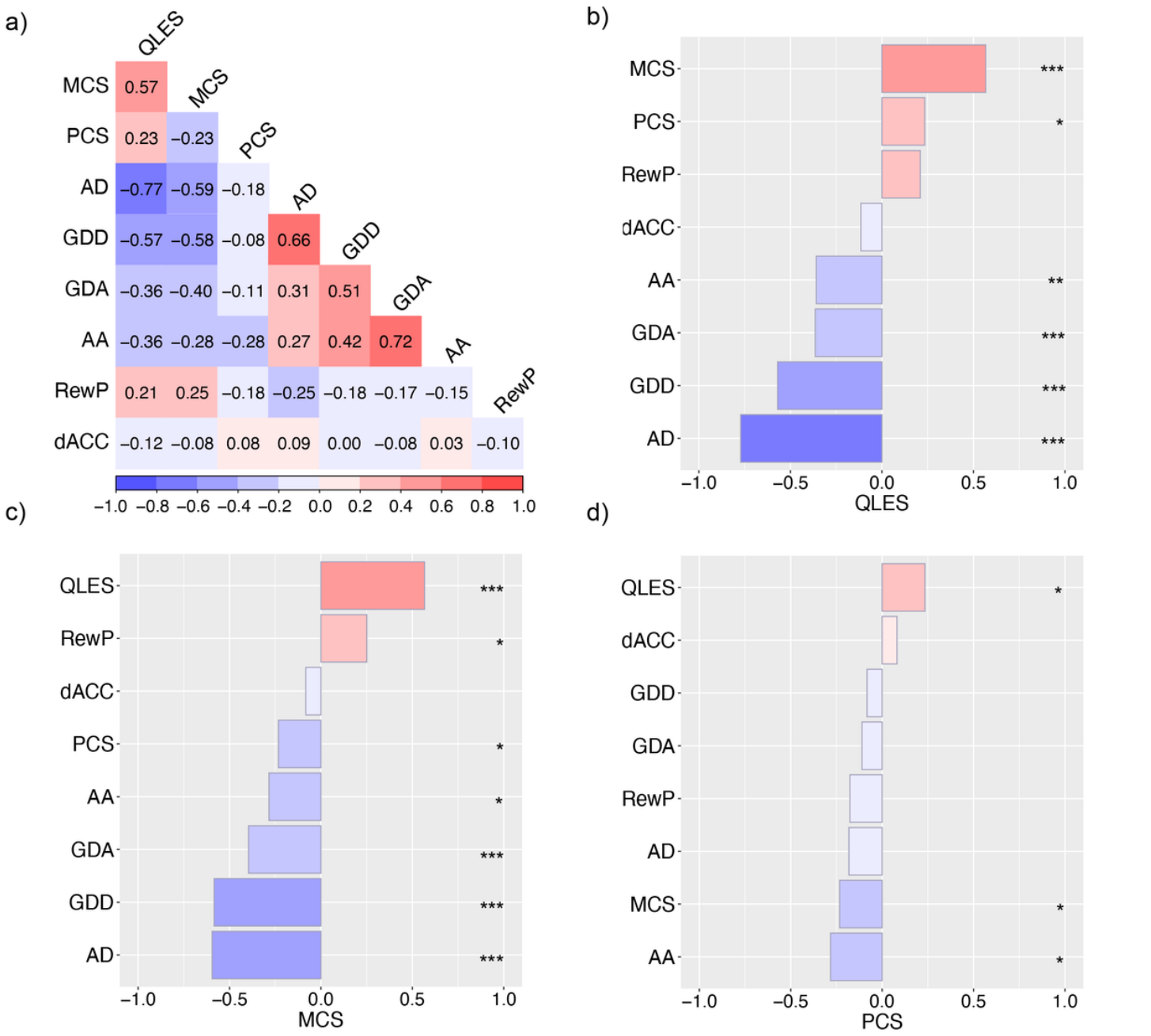

Figure 2

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. Asterisks on panels 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.

Note. 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.

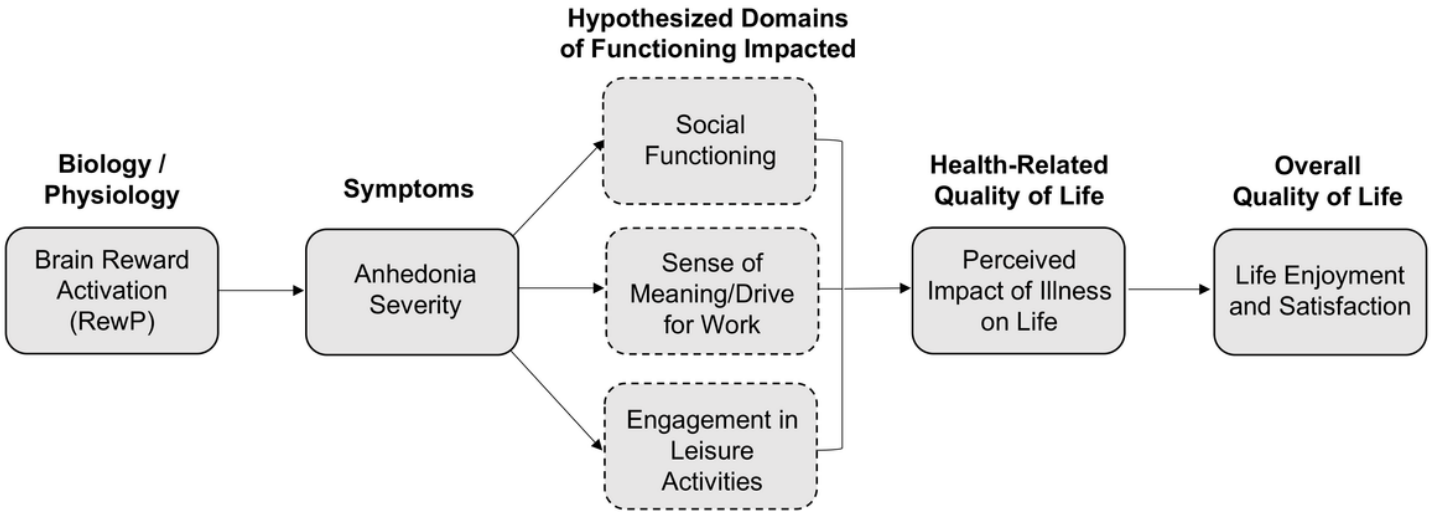

Figure 3

Schematic showing the potential pathways via which brain reward function may be linked to patient's overall quality of life. Domains of functioning (denoted by dashed borders) were not directly evaluated in this study, so have been inferred from prior research. This schematic was informed by Wilson & Cleary's (1995) Conceptual Model of Patient Outcomes, which shows the pathways through which biological/physiological measures may influence patient quality of life via symptoms, functioning and health perceptions.

Supplementary Files

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- RDoCQoLSupplement11062022.docx