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Depression and anxiety mediate the relationship between frontotemporal white matter integrity and quality of life in distressed young adults

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Abstract

Depression and anxiety have been linked to poor quality of life (QoL) – one's subjective perception of relationships, physical health, daily functioning, general sense of well-being and life satisfaction. Elucidating abnormal white matter microstructure associated with mood and other symptoms and QoL is important to facilitate treatment. Ninety-six young adults (18–25 years old) seeking help for psychological distress, irrespective of presence or absence of psychiatric diagnosis completed diffusion weighted and anatomical scans, clinical and behavioral measures, and QoL assessment. We examined relationships between diffusion imaging properties in major white matter tracts involved in emotion processing and regulation, symptoms, and QoL. Depression and general distress levels fully mediated the relationship between fractional anisotropy (FA), an indirect index of fiber collinearity, and radial diffusivity (RD), an index sensitive to axonal/myelin damage, in right uncinate fasciculus and QoL. The relationship between reduced FA (and increased RD) in right uncinate fasciculus and poor QoL was explained by greater severity of depression and general distress. These findings underscore the role of white matter microstructure in right uncinate fasciculus in relation to depressive and general distress symptoms and, in turn, QoL. Importantly, they suggest that measures of white matter microstructure in this tract can be used as putative objective markers of emotion dysregulation, to inform and monitor the impact of interventions to reduce affective symptoms and improve QoL in young adults.

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Author contributions

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.10.001.

Keywords

Diffusion; Fractional anisotropy; Uncinate fasciculus; Mediation; Symptoms

1. Introduction

Depression and anxiety are prevalent in early adulthood and have been linked to poor quality of life (QoL) – one's subjective perception of relationships, physical health, daily functioning, general sense of well-being and life satisfaction (Endicott et al., 1993). QoL has become an important target of treatment and criterion of treatment outcome (Dzevlan et al., 2019).

Elucidating abnormal neural function and structure associated with mood and other symptoms and poor QoL could facilitate treatment. However, few studies examined relationships between neural measures, clinical symptoms, and QoL. Previously, we reported that the relationship between amygdala and left ventrolateral prefrontal cortex activity during emotion processing and QoL is mediated by anxiety (Greenberg et al., 2017). These findings indicate that relationships between neural activity and QoL can be explained by anxiety severity and provide a first step towards identification of neural targets for intervention to reduce anxiety and improve QoL.

There is growing evidence for alterations in white matter microstructure in relation to affective symptoms. In general, studies have reported reductions in fractional anisotropy (FA), an indirect index of fiber collinearity, in symptomatic versus healthy individuals (Jenkins et al., 2016; van Velzen et al., 2020). For example, reduced FA in the uncinate fasciculus, a tract connecting the orbitofrontal cortex to anterior temporal lobes, and implicated in emotion processing and regulation, has been repeatedly observed in depressed individuals (Bracht et al., 2015; Dillon et al., 2018), and in anxious individuals (Phan et al., 2009).

In the current study, we aimed to extend our previous findings that linked neural activity and QoL (Greenberg et al., 2017) by examining directional relationships between white matter microstructure, behavioral/clinical measures, and QoL in young adults with a range of symptoms and problem behaviors (including depressive and anxiety symptoms and difficulties in coping with everyday stressors and interpersonal relationships). We used elastic-net penalized regressions and follow-up simple linear regressions to identify behavioral/clinical symptoms associated with both QoL and mean FA in major tracts involved in emotion processing and regulation (Lai and Wu, 2014; Versace et al., 2015). We then determined the extent to which these identified behavioral/clinical measures mediated the relationship between mean FA and QoL. Based on our previous work (Greenberg et al., 2017) and present literature, we hypothesized that:

1. Mean FA in key tracts involved in emotion processing and regulation would be negatively associated with depressive and/or anxiety symptoms and positively associated with QoL.

2. Depressive and/or anxiety symptoms would mediate the relationship between mean FA and QoL.

2. Methods

2.1. Participants

Participants were 96 individuals (70 females), 18–25 years old, seeking help for psychological distress including depressive and anxiety symptoms, irrespective of presence or absence of psychiatric diagnosis (Supplementary Table 1s). Exclusion criteria for the study were: history of head injury, neurological, pervasive developmental disorder or systemic medical disease, cognitive impairment (Mini-Mental State Examination (Folstein et al., 1975) score < 24), and premorbid North American Adult Reading Test (NAART; Blair and Spreen, 1989) IQ estimate < 85, visual disturbance (< 20/40 Snellen visual acuity), left or mixed handedness (Annett criteria; Annett, 1970), alcohol/substance use disorder (SUD, including nicotine) and/or illicit substance use (except cannabis) over the last 3 months determined by the Structured Clinical Interview for DSM-5, Research Version (First et al., 2015) and current use tested with urine and saliva tests. Additional MRI exclusion criteria were: positive pregnancy test/report for female participants, and any current psychotropic medication use for > 2 weeks. Previous medication was allowed, but individuals needed to be free from such medication for at least 3 months. The study was conducted in accordance with the Declaration of Helsinki and approved by the University of Pittsburgh Human Research Protection Office. All participants provided informed consent.

2.2. Behavioral/clinical measures

Participants were assessed on measures that examine symptoms and problem behaviors common in young adults (see Table 1): Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960); Mood and Anxiety Symptom Questionnaire, including the general distress anxiety subscale (MASQ-GA), general distress depression subscale (MASQ-DA), general distress mixed subscale (MASQ-GDM), anxious arousal subscale (MASQ-AA), and anhedonic depression subscale (Clark and Watson, 1991); the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959), Spielberger State-Trait Anxiety Inventory (Spielberger et al., 1970); Zuckerman sensation seeking scale (Zuckerman, 2007); Behavioral Inhibition and Activation System Scales BIS/BAS (Carver and White, 1994); Barratt Impulsiveness Scale (Patton et al., 1995); UPPS-P Impulsive Behavior Scale (Whiteside and Lynam, 2001); and Young Mania Rating Scale (Young et al., 1978). Participants also completed the Quality of life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF) to assess their perception of life enjoyment and satisfaction (Endicott et al., 1993).

2.3. Image acquisition

Neuroimaging data (96 total) were collected on a 3T Siemens Prisma (n = 68) or a 3T Siemens Trio (n = 28) using the same imaging protocol, at the Magnetic Resonance Research Center (MRRC) in the University of Pittsburgh Medical Center. We acquired a single-shot spin-echo echo planar imaging (SE-EPI) sequence 197 diffusion-weighting gradient directions (32 vol with b = 700 s/mm^2, 65 vol with b = 1000 s/mm^2, 100 vol with b = 2500 s/mm^2) and 13 reference volumes with b = 0 s/mm^2 (repetition time (TR)

= 3000 ms, echo time (TE) = 120 ms, flip angle = 90°, field-of-view (FOV) = 256 × 256, 2 mm^3 isotropic voxel, simultaneous multi-slice (SMS) factor = 4, acquisition time = 630 s). The sequence was collected twice with opposite phase encoding directions (Posterior > Anterior and Anterior > Posterior) to reduce EPI distortions (Andersson and Sotiropoulos, 2015, 2016). We also acquired structural 3D axial MPRAGE images (TR = 1500 ms, TE = 3.19 ms, flip angle 8°, FOV = 256 × 256 mm, 1 mm^3 isotropic voxels, 176 continuous slices).

2.4. Diffusion data analysis

Diffusion-weighted images were corrected for eddy current, subject motion and EPI distortion using topup and eddy (Andersson et al., 2003; Andersson and Sotiropoulos, 2015, 2016; Smith et al., 2004) within FMRIB's Software Library (FSL 6.0). Using a triple-tensor model, as proposed in (Behrens et al., 2007; Jbabdi et al., 2012) and a global probabilistic tractographic approach, white-matter tracts were reconstructed with Tracts Constrained by Underlying Anatomy (TRACULA; Yendiki et al., 2011), the diffusion imaging toolbox of the FreeSurfer package (https://surfer.nmr.mgh.harvard.edu). For each participant, following visual inspection of reconstructed tracts, we extracted diffusion tensor measures estimated with *dtifit*, including mean fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD), in 13 white matter tracts implicated in emotion processing and regulation (Lai and Wu, 2014; Versace et al., 2015): forceps minor and right/left uncinate fasciculus, cingulum cingulate gyrus, cingulum angular bundle, superior longitudinal fasciculus - parietal endings, superior longitudinal fasciculus - temporal endings, and inferior longitudinal fasciculus (Supplementary Figure 2s).

2.5. Statistical analysis plan

We conducted elastic-net penalized least squares regression analyses (GLMNET package in R; Friedman et al., 2014) with $\alpha = 0.5$ and 10-fold cross-validation, sex, scanner, age and National Adult Reading Test (NART) scores as covariates, and follow-up simple linear regressions, to identify variables for a mediation analysis using three steps: 1) FA measures (one per tract = 13 total) related to QoL. 2) behavioral/clinical measures (33 total) related to FA measures identified in step 1, and 3) behavioral/clinical measures (identified in step 2) related to QoL.

We then examined the extent to which behavioral/clinical measures associated with both QoL and FA measures mediated relationships between FA and QoL using PROCESS version 3.4 (Hayes and Little, 2018). We computed bootstrapped confidence intervals (BootCI) for all variables with 5000 samples and 95% level of confidence.

To aid FA findings interpretation, we conducted a secondary analysis using RD, AD, and MD measures in those tracts in which mean FA showed a significant relationship with QoL and behavioral/clinical measures.

3. Results

3.1. FA measures related to QoL (step 1)

One FA measure was identified as a non-zero predictor of poor QoL with elastic-net regression: lower FA in right uncinate fasciculus (i.e., lower FA in right uncinate fasciculus was associated with poorer QoL). The exponentiated coefficient (exp) = 2.017, which represents the ratio change in outcome variable (i.e., QoL) corresponding to one-unit change in predictor variable. A follow-up simple linear regression showed a significant positive association between right uncinate fasciculus FA and QoL ($b = 1.87$, $F_{(1,94)} = 5.82$, $p = 0.018$; Supplementary Figure 2s).

3.2. Behavioral/clinical measures related to FA measures (step 2)

Three clinical measures were identified as non-zero predictors of lower FA in right uncinate fasciculus with elastic-net regression: greater HAM-D (exp = 0.974), MASQ-GDM (exp = 0.9995), and BIS (exp = 1.008). Namely, increased depressive symptoms, general distress, and behavioral avoidance (inhibition) were associated with lower FA in right uncinate fasciculus. Follow-up simple linear regressions, conducted for each of these clinical measures using Bonferroni adjusted alpha levels of .0167 per test (0.05/3), showed a significant negative association between HAM-D ($b = -0.052$, $F_{(1,94)} = 12.09$, $p = 0.001$; Supplementary Figure 3s) and MASQ-GDM ($b = -0.023$, $F_{(1,94)} = 6.85$, $p = 0.01$; Supplementary Figure 4s) and FA in right uncinate fasciculus, but not BIS ($p = 0.217$).

3.3. Behavioral/clinical measures related to QoL (step 3)

We conducted simple linear regressions with HAM-D and MASQ-GDM (the only clinical measures significantly associated with right uncinate fasciculus FA) as independent variables and QoL as the dependent variable using Bonferroni adjusted alpha levels of 0.025 per test (0.05/2).Increased depressive symptoms (b = −0.65, $F_{(1,94)} = 39.06$, $p < 0.001$; Supplementary Figure 5s) and general distress levels (b = −0.383, $F_{(1,94)} = 44.81$, $p < 0.001$; Supplementary Figure 6s), were associated with poorer QoL.

3.4. Testing regression assumptions and outliers for the mediation model

We tested normality of residuals, homoscedasticity, absence of multicollinearity and outlier tests of Mahalanobis, Cook's, and Leverage values. Examination of Predicted Probability (P–P) plots showed normality of residuals and homoscedasticity. Residuals were independent, the Durbin Watson statistic (d) = 2.032, and the Variance Inflation Factor (VIF), a measure of multicollinearity was < 2. There were no cases that warranted exclusion (i.e. no cases had extreme values on two of the three outlier tests).

3.5. Mediation

We conducted a parallel mediation model (PROCESS version 3.4, model 4; Hayes and Little, 2018) to simultaneously test HAM-D and MASQ-GDM, the only clinical variables significantly associated with both QoL and white matter microstructure, as potential mediators of the relationship between right uncinate fasciculus FA and QoL.

The coefficients in this multiple mediator model reflect the amount of mediation for each variable after accounting for the other mediator in the model.

HAM-D and MASQ-GDM fully mediated the positive relationship between right uncinate fasciculus FA and QoL [$t_{(94)}$ = 2.41, p = 0.018 (total effect) going to $t_{(94)}$ = 0.6302, p = 0.53 (direct effect); Fig. 1]. There were significant negative relationships between right uncinate fasciculus FA and HAM-D ($t_{(94)}$ = −3.48, p = 0.0008, BootCI = −3.53 to −0.848) and MASQ-GDM ($t_{(94)}$ = −2.62, p = 0.0103, BootCI = −5.38 to −0.748), and between HAM-D and MASQ-GDM and QoL ($t_{(92)}$ = −2.25, p = 0.027, BootCI = −0.576 to −0.064; $t_{(92)}$ = −3.18, p = 0.002, BootCI = −0.398 to −0.0998, respectively). The indirect (i.e. mediated) effects between right uncinate fasciculus FA and QoL, through HAM-D and MASQ-GDM, were significant (i.e. did not include zero; BootCI = 0.074 to 1.62 and BootCI = 0.139 to 1.58, respectively).

3.6. Mediation: Alternative pathway

Right uncinate fasciculus FA did not mediate the relationship between HAM-D or MASQ-GDM, and QoL.

3.7. Relationships between RD, MD, and AD in right uncinate fasciculus and HAM-D, MASQ-GDM, and QoL

Higher right uncinate fasciculus RD was associated with increased HAM-D ($r_{(96)}$ = 0.405, p < 0.001) and MASQ-GDM ($r_{(96)}$ = 0.29, p = 0.004) scores. In addition, we observed a nonsignificant trend for an association between higher right uncinate fasciculus RD and poorer QoL ($r_{(96)}$ = −0.188, p = 0.066). A follow-up mediation analysis showed that HAM-D and MASQ-GDM fully mediated the negative relationship between right uncinate fasciculus RD and QoL (Supplementary Fig. 7s).

Higher right uncinate fasciculus MD was associated with increased HAM-D ($r_{(96)}$ = 0.33, p = 0.001) and MASQ-GDM ($r_{(96)}$ = 0.21, p = 0.043) scores. We did not observe a significant association between right uncinate fasciculus MD and QoL ($r_{(96)}$ = −0.117, p = 0.26).

There were no significant associations between right uncinate fasciculus AD and either HAM-D, MASQ-GDM, or QoL (all ps > 0.1).

4. Discussion

We show directional relationships between white matter microstructure, symptoms, and QoL in distressed young adults regardless of diagnosis. HAM-D and MASQ-GDM fully mediated the relationship between FA and RD in right uncinate fasciculus and QoL. Specifically, the relationship between reduced FA (and increased RD) in right uncinate fasciculus and poor QoL was explained by greater severity of depression and general distress.

Reduced FA in uncinate fasciculus has been observed most commonly in depression (Bracht et al., 2015), but also anxiety (Phan et al., 2009) and psychopathy (Motzkin et al., 2011). Here, we showed a negative (i.e. inverse) relationship between FA in right uncinate fasciculus (and a positive relationship for right uncinate fasciculus RD), and both depression

and general distress levels (derived from depressive and anxiety symptoms). This supports a broader role for this tract in emotional dysregulation. Variations in uncinate fasciculus FA and RD, which are indirect indices of white matter integrity, suggest decreased connectivity that may disrupt prefrontal control over limbic regions, including the amygdala, thereby contributing to elevated affective symptoms, and in turn, poor QoL.

Participants' levels of depression and general distress were most predictive of QoL consistent with findings demonstrating substantial QoL impairments in depressed and anxious individuals (Olatunji et al., 2007; Rapaport et al., 2005). QoL is an important measure of treatment outcome, that is related but not redundant with symptom severity (Endicott et al., 1993), and encompasses a range of psychosocial and physical factors of life satisfaction from the patient's perspective (Dzevlan et al., 2019).

The strengths of this study are: the focus on early adulthood – an important neurodevelopmental period, and the transdiagnostic approach. The main limitation is the cross-sectional design that precludes causal inferences. Future studies should further examine relationships between white matter microstructure in uncinate fasciculus, symptoms, and QoL using measures that capture localized differences, and investigate whether developmental changes in this tract predict levels of QoL over time.

Together, our findings highlight the role of white matter microstructure in right uncinate fasciculus in relation to depressive and general distress symptoms, and, in turn, QoL. Furthermore, they suggest that measures of white matter microstructure in this tract can be used as putative objective markers of emotion dysregulation, to inform and monitor the impact of interventions to reduce mood and anxiety symptoms and improve QoL in young adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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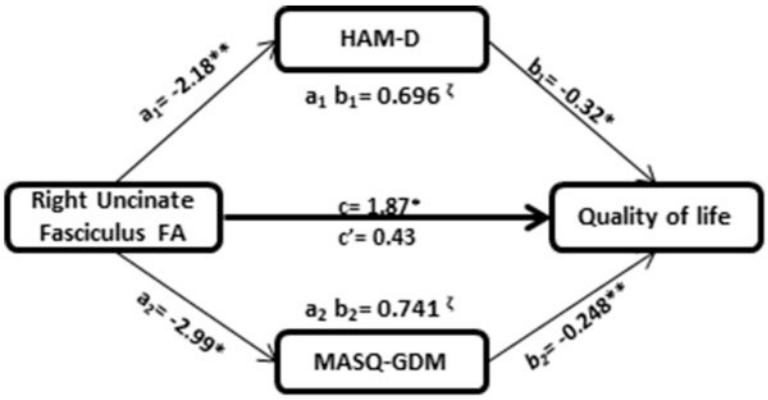

a_1: causal effect of X on M_1
a_2: causal effect of X on M_2
c: direct effect of X on Y
c': mediated effect of X on Y
b_1: effect of M_1 on Y
b_2: effect of M_2 on Y
M1 = Hamilton Rating Scale for Depression (HAM-D)
M2 = Mood and Anxiety Symptom Questionnaire, general distress mixed subscale (MASQ-GDM)
X = Right Uncinate Fasciculus Mean Fractional Anisotropy (FA)
Y = Quality of life
a_1 b_1: specific indirect effect of M_1 on the relationship between X and Y
a_2 b_2: specific indirect effect of M_2 on the relationship between X and Y
* p<.05
** p<.005
ζ 95% confidence interval does not contain 0.
Solid line: significant relationship
Heavy sold line: full mediation

Fig. 1.

A parallel mediation model examining the effect of Hamilton Rating Scale for Depression (HAM-D) and the Mood and Anxiety Symptom Questionnaire, general distress mixed subscale (MASQ-GDM) scores on the relationship between mean fractional anisotropy (FA) in right uncinate fasciculus and quality of life (QoL).

Table 1

Demographic and Clinical/Behavioral Data (n = 96; 70 females/26 males).

Characteristic Mean (SD)	
Age (years)	21.6 (2.1)
National Adult Reading Test score	109.23 (7.08)
Clinical and behavioral measures [a]	
Hamilton Depression Rating Scale (17-item)	14.65 (6.18)
Mood and Anxiety Symptom Questionnaire general distress mixed subscale	41.22 (10.99)
Behavioral Inhibition and Activation System: Inhibition subscale	23.37 (3.23)
Quality of life Enjoyment and Satisfaction Questionnaire - Short Form	45.38 (7.41)

[a]Results for all 33 clinical and behavioral measures used in the elastic net analysis are in Supplementary Table 2s.